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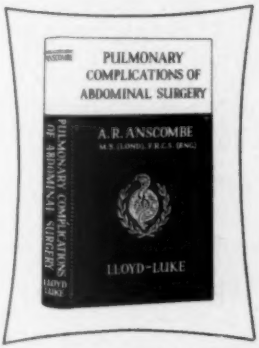

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The very wide range of exhibits by many leading British firms will include ethical medical preparations, surgical instruments, medical equipment, books, hospital equipment, etc., and will demonstrate the latest developments in medical practice. There will be daily performances of films selected for their exceptional medical interest, and facilities will be provided on the premises for obtaining light meals and refreshments. Copies of the invaluable reference book, The London Medical Handbook, will be available to visitors at the specially reduced price of 2s. 6d.

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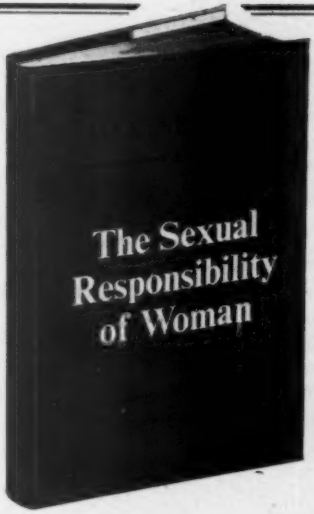

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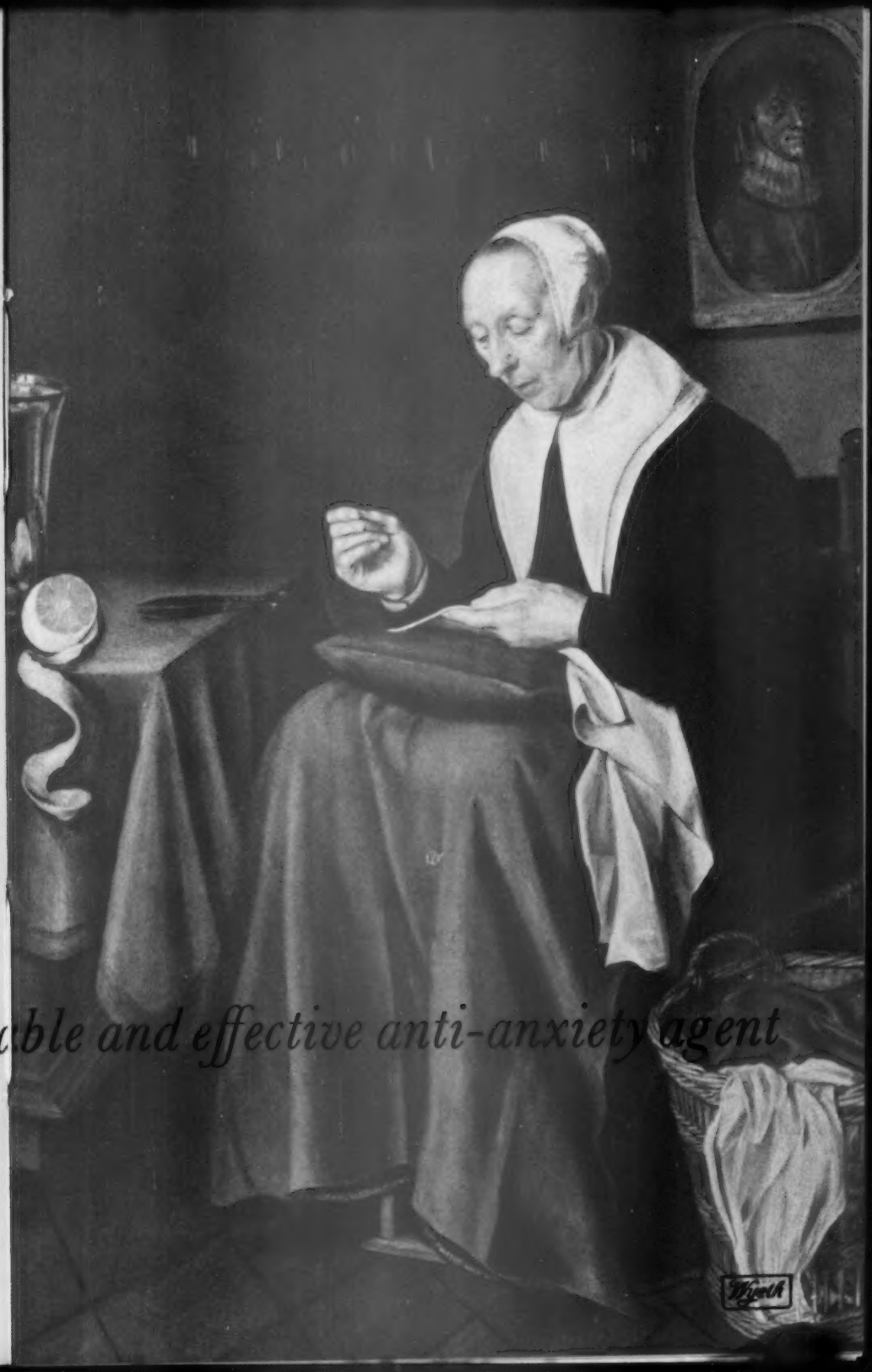
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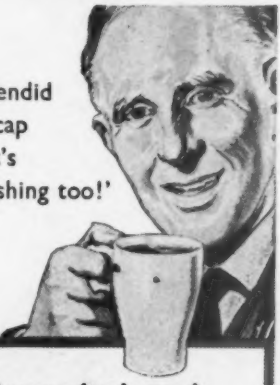

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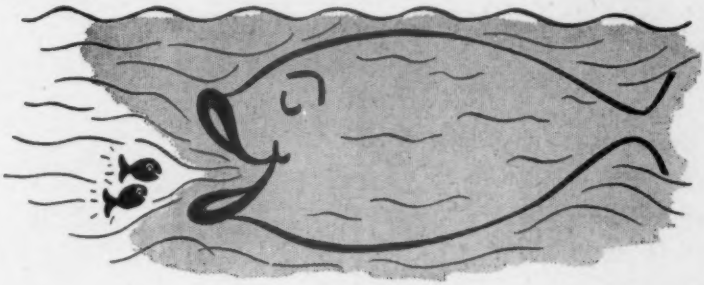

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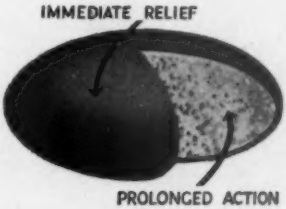

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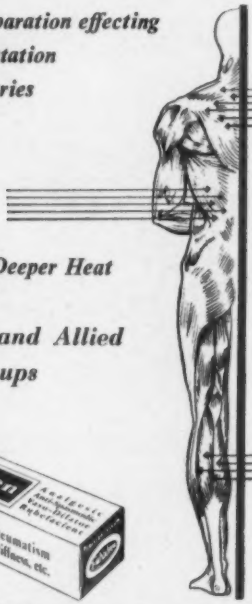
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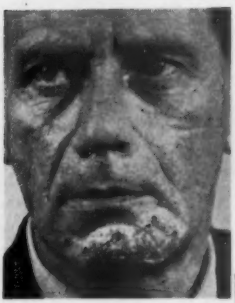

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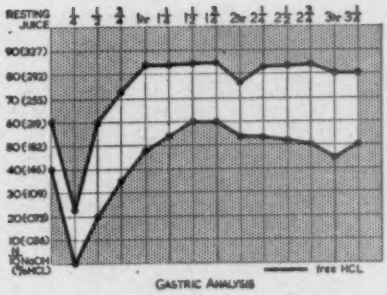

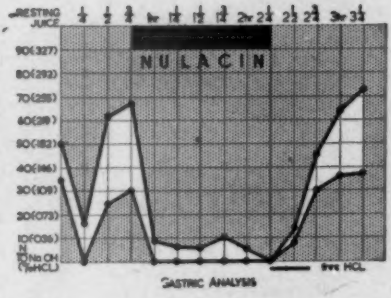

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SELECTED REFERENCES

Antacids, *The Practitioner*, January, 1957, **178:** 43

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The Control of Gastric Acidity, *Brit. Med. J.*, 26th July, 1952, **2:** 180-182

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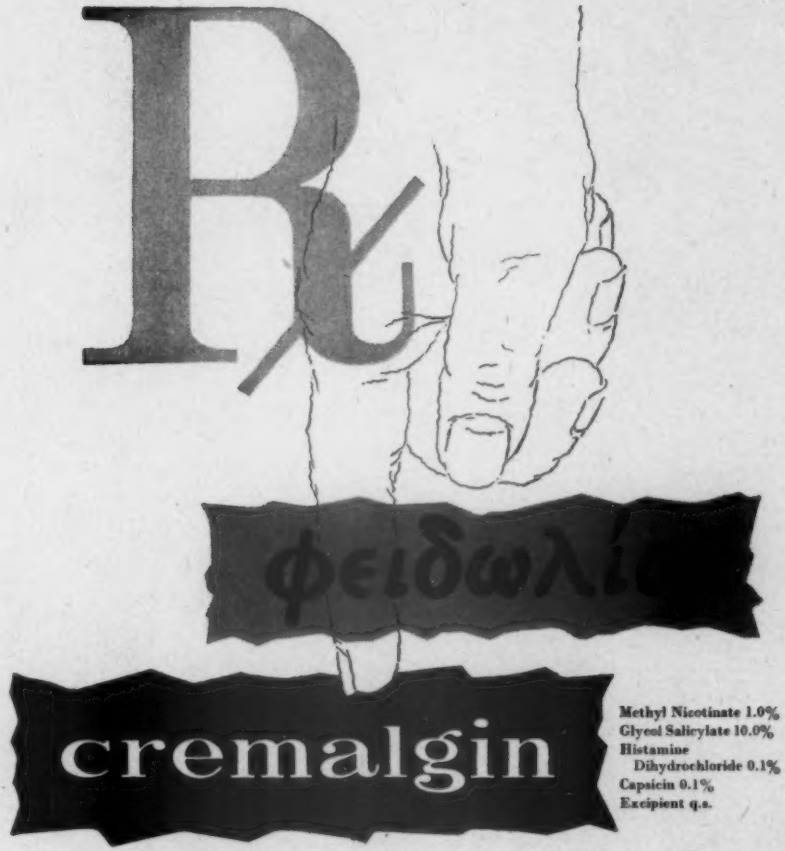

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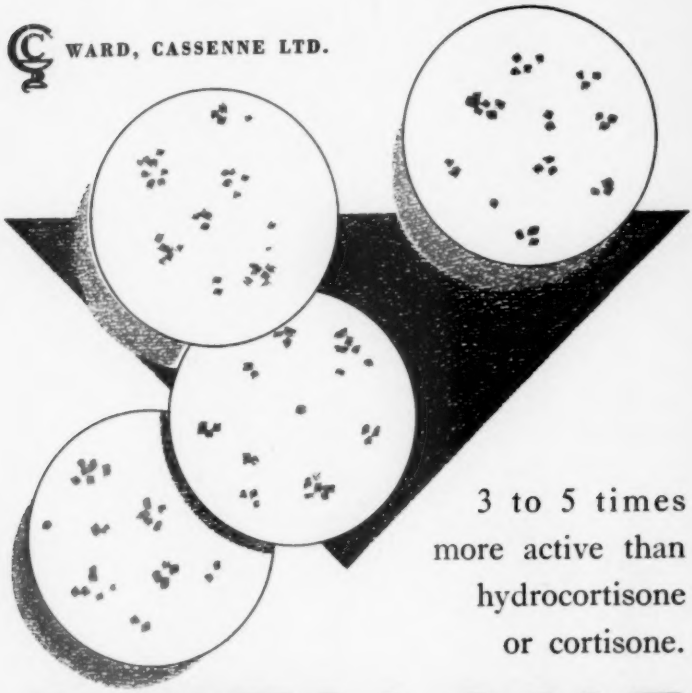

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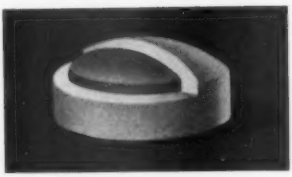

A new concept in therapy with Prednisone and Prednisolone— Buffered Protection against gastric distress

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'CO-DELTRA' or 'CO-HYDELTRA' should be prescribed whenever Prednisone or Prednisolone is indicated, in order to minimise gastric distress.

REFERENCES

1. The Lancet, Nov. 12th 1955, p.993
2. The Lancet, Jul. 7th 1956, p.18
3. B.M.J., Jan. 26th 1957, p.215
4. B.M.J., Feb. 2nd 1957, p.271
5. The Lancet, Feb. 9th 1957, p.312

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'Co-Deltra' (Prednisone, buffered) and 'Co-Hydeltra' (Prednisolone, buffered) Multiple Compressed Tablets are supplied in bottles of 100.

It is now universally accepted that oral therapy with Cortisone, Hydrocortisone, Prednisone or Prednisolone is frequently accompanied by hyperacidity and gastric distress which may eventually result in peptic ulcer with its possible dangerous complications.[1-5]

'CO-DELTRA' and 'CO-HYDELTRA' contain a solid inner core of Prednisone or Prednisolone and an outer coating consisting of the antacids Magnesium Trisilicate and Aluminium Hydroxide. On contact with the gastric secretions the outer coat of antacids is released to neutralise excessive acid, and only then is the active steroid brought into contact with the gastric mucosa. Furthermore, the buffering effect of the antacids will minimise any gastric distress which may result from local irritation due to the steroid.

MERCK SHARP & DOHME LIMITED, HODDESDON, HERTS. MSD

FIRST oral trichomonacide

TRITHEON*

BRAND OF AMINITROZOLE TABLETS TRADE MARK

for male and female.

Because of their systemic action, **TRITHEON** tablets reach resistant trichomonads in their hiding places throughout the genito-urinary tract. Unlike local trichomonacides, **TRITHEON** tablets eradicate the organism in male and female as proved by *negative culture*.

Clinical investigation has demonstrated that **TRITHEON** tablets administered orally eradicate trichomonads for **culture-proved cure** of more than 70 per cent of female patients whose husbands are treated simultaneously with **TRITHEON** tablets. Even when only the wife is treated, cures are effected in approximately one-third of the patients.

Dosage: One tablet three times daily for 10 days

Available: Bottles of 30, 180 and 1000 tablets; each tablet contains 100mg 2-acetylamino-5-nitrothiazole

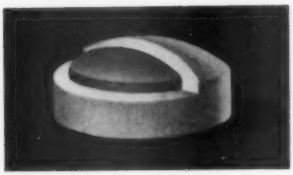
LITERATURE ON REQUEST

Ortho

Ortho Pharmaceutical Limited • High Wycombe • England

* **TRITHEON** is the original brand of 2-acetylamino-5-nitrothiazole tablets developed in the Ortho Research Foundation for the oral treatment of trichomoniasis

A TABLET WITHIN A TABLET



A new concept in therapy with Prednisone and Prednisolone—
Buffered Protection
against gastric distress

TRADE MARK

CO-DELTRA
(Prednisone, buffered)

&

TRADE MARK

CO-HYDELTRA
(Prednisolone, buffered)

'CO-DELTRA' or 'CO-HYDELTRA'
should be prescribed whenever Prednisone or Prednisolone is indicated, in order to minimise gastric distress.

REFERENCES

1. The Lancet, Nov. 12th 1955, p.993
2. The Lancet, Jul. 7th 1956, p.18
3. B.M.J., Jan. 26th 1957, p.215
4. B.M.J., Feb. 2nd 1957, p.271
5. The Lancet, Feb. 9th 1957, p.312

HOW SUPPLIED:
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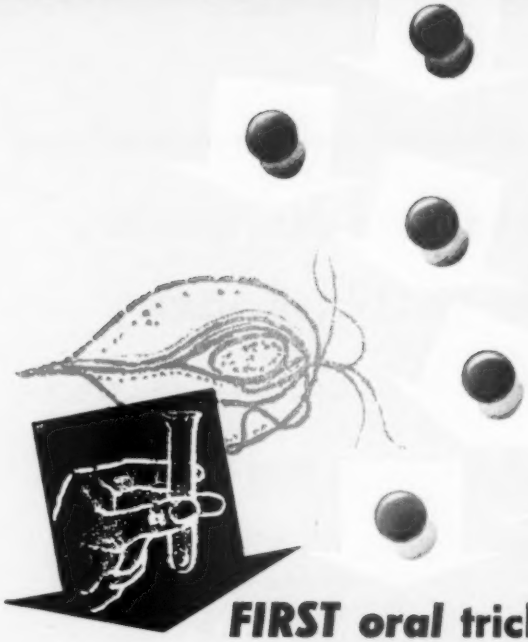
MERCK SHARP & DOHME LIMITED, HODDESDON, HERTS. MSD



FIRST oral trichomonacide

TRITHEON*

BRAND OF AMINITROZOLE **TABLETS** TRADE MARK

for male and female.

Because of their systemic action, **TRITHEON** tablets reach resistant trichomonads in their hiding places throughout the genito-urinary tract. Unlike local trichomonacides, **TRITHEON** tablets eradicate the organism in male and female as proved by *negative culture.*

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Ortho Pharmaceutical Limited • High Wycombe • England

* **TRITHEON** is the original brand of 2-acetylamino-5-nitrothiazole tablets developed in the Ortho Research Foundation for the oral treatment of trichomoniasis

During winter months, your patients with chronic bronchitis can be kept up-and-about, free from distressing symptoms, by the prophylactic use of

TEDRAL

TRADE MARK

Active Principles: Theophylline 2 gr. (120 mg) Ephedrine hydrochloride ¾ gr. (25 mg) Phenobarbitone ⅛ gr. (8 mg).

℞ one tablet every four hours

WILLIAM R. WARNER & CO. LTD., POWER ROAD, LONDON, W.4.

a completely **new** vaginal gel

for the treatment of Vaginitis due to

TRICHOMONAS

MONILIA

AND

BACTERIA

including Haemophilus Vaginalis, the organism responsible for some of the so called "non-specific" infections.

sterisil

TRADE MARK

Administration: One applicatorful (7 ml.) instilled into the vagina every other night. Clinical cure may result from six applications, but twelve applications, should be advised.

Presentation: Sterisil is available in boxes containing a tube of vaginal gel (1½ oz.) and six disposable applicators.

Active Principle: Hexetidine 0.1%

WM. R. WARNER & CO. LTD., WARNER **POWER ROAD, LONDON, W.4.**

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Distinguished Record

Three years of clinical use have given 'Ilotycin' brand Erythromycin a distinguished record of remarkable safety. Highly effective against staphylococci, streptococci and pneumococci, 'Ilotycin' exerts negligible effect on the colon bacillus and does not give rise to the extremely dangerous staphylococcal enterocolitis. It is particularly valuable against penicillin-resistant staphylococci and has become the logical first choice antibiotic after penicillin. 'Ilotycin' is the surest and safest way of combating a wide range of common infections encountered in general and hospital practice, and can be life-saving in overwhelming infections where prompt response is vital.

The average daily dose is 1 Gm., increased in severe infections.

'Ilotycin' is available as Tablets of 100 mg. and 250 mg., and as 'Ilotycin' Paediatric for oral suspension.

Lilly

'ILOTYCIN'

Originated by Lilly

ELI LILLY AND COMPANY LIMITED, BASINGSTOKE, ENGLAND

SEBORRHOEIC DERMATITIS

PRAGMATAR

highly effective in a wide range of skin disorders

a versatile and safe preparation containing tried and proved agents for the treatment of *seborrhoeic dermatitis* (including *cradle cap*), *eczematous eruptions*, *psoriasis*, *fungous infections* and *dandruff*

Pragmatar — cetyl alcohol-coal-tar distillate, sulphur and salicylic acid

Smith Kline & French Laboratories Ltd.
Coldharbour Lane, London, SE5

'Pragmatar' is a registered trade mark

PR:PA27 (Col)

Here's a girl who knows how to enjoy life. You wouldn't think she has much to worry about, yet she's going into hospital tomorrow for an operation. That's just about it: she has *nothing* to worry about. Without giving it a thought, she relies on the skill and experience of doctors and nurses; and they, in their turn, rely on British Oxygen equipment and gases. In thousands of cases, every day, British Oxygen equipment and gases are used to ease pain and to save lives.

BOC **BRITISH OXYGEN**

BRITISH OXYGEN GASES LIMITED, MEDICAL DIVISION, GREAT WEST ROAD, BRENTFORD, MIDDLESEX

Makers and suppliers of anaesthetic, analgesic and therapeutic equipment and gases

milder

greatest

CORDEX

Upjohn

escape
from
the
agony
of
abdominal **spasm**

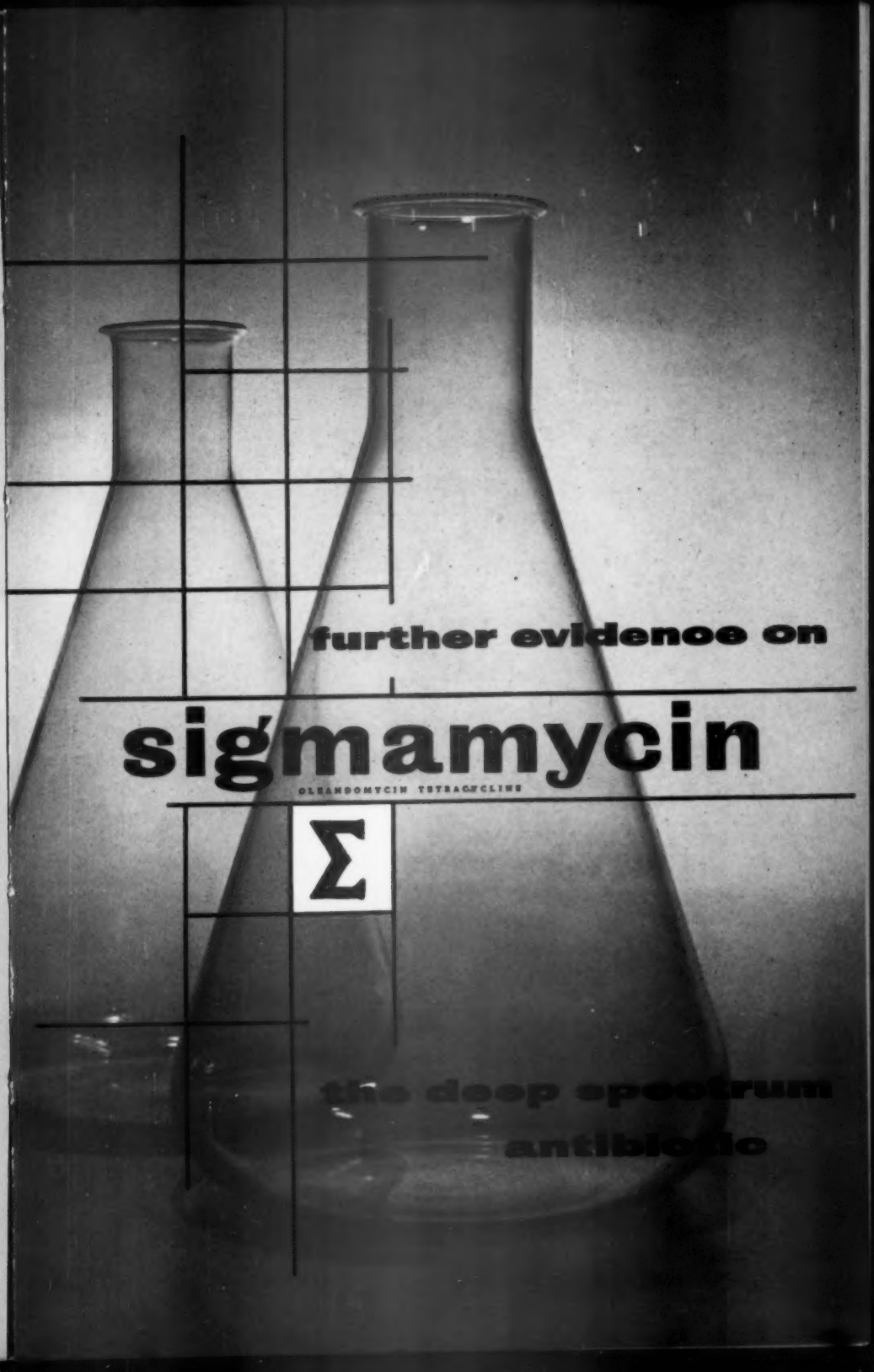
BUSCOPAN is a spasmolytic with a rapid and safe action upon the hollow organs of the abdomen Virtually free from side effects with a selective action and low toxicity, BUSCOPAN can be used wherever spasm causes or prolongs disorders of the hollow organs. It will give almost immediate relief from pain and serve as an aid to treatment.

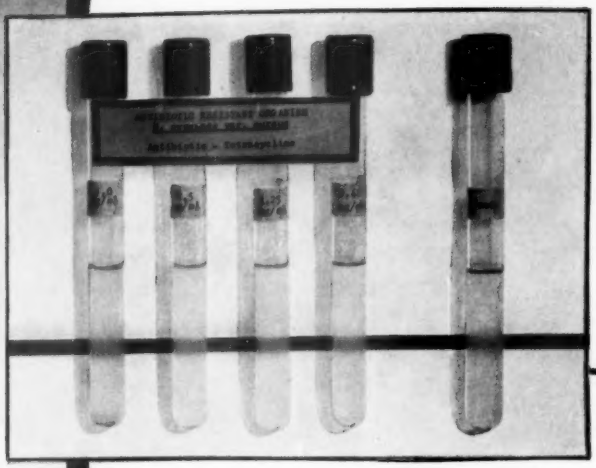
BUSCOPAN *

HYOSCINE-N-BUTYLBROMIDE

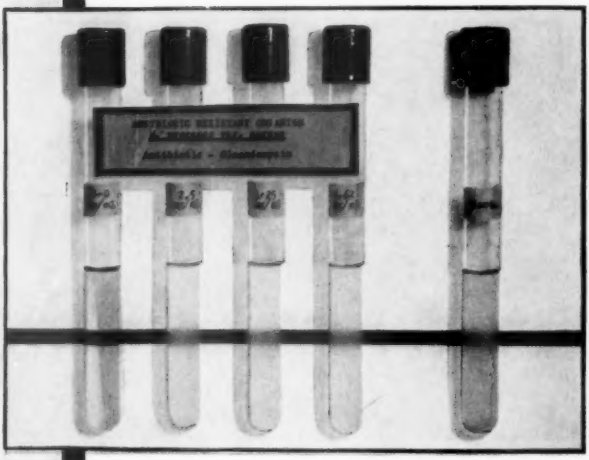
Manufactured and distributed in England
by Pfizer Ltd., Folkestone, Kent, for
C. H. Boehringer Sohn, Ingelheim am Rhein
Registered proprietors of the Trade Mark

* Regd. Trade Mark


further evidence on
sigmamycin
OLEANDOMYCIN TETRACYCLINE
Σ
the deep spectrum
antibiotic



Tetracycline—no inhibition at any level



Oleandomycin—inhibition only at 5.0 mcg/ml.

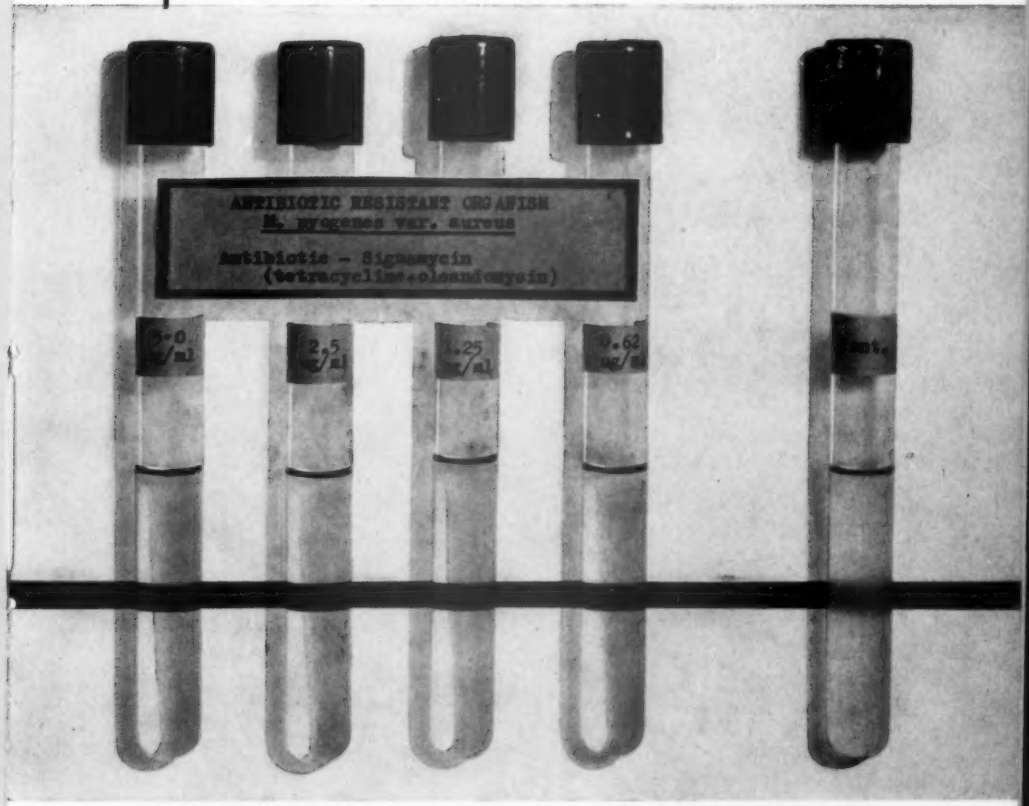
These photographs show one of a series of tests made with SIGMAMYCIN and its components against a number of antibiotic resistant clinical isolates of Staphylococcus Aureus. The results of this test, and all the other data so far received, show clearly that SIGMAMYCIN is markedly more active than either of its components, and exhibits *true synergism.*

sigmamycin*

OLEANDOMYCIN TETRACYCLINE

Σ

a demonstration of enhanced activity



Sigmamycin — inhibition at ALL levels

INDICATIONS

Indications for Sigmamycin fall under three main headings.

1. Infections due to organisms sensitive to one or both of its components.[1]

2. Infections due to unidentified organisms, when the maximum range of effectiveness, potency of action, and tolerance is required.

3. Infections, identified or not, which have already shown resistance to other chemotherapeutic agents.

DOSAGE

Dosage with Sigmamycin varies with the type of infection, its severity, and the age and weight of the patient. Normal dosage for a moderate infection is one 250 mg. capsule every six hours. In severe infections this may be increased to two capsules every six hours, while in fulminating infections a further increase may be needed.

AVAILABILITY

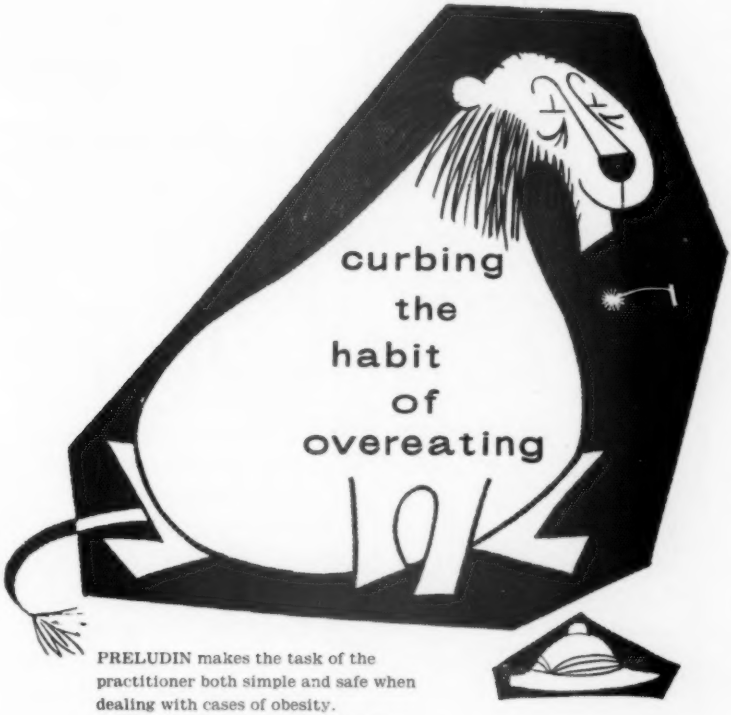
Sigmamycin capsules, each containing 167 mg. tetracycline and 83 mg. oleandomycin, are available in bottles of 16 and 100.

[1]Tetracycline is effective against Gram-positive and Gram-negative bacteria, Rickettsiæ, spirochætes, large viruses, and the protozoa *Entamœba histolytica*. Oleandomycin has shown activity against Gram-positive organisms, including pneumococci, streptococci, and staphylococci, and against certain Gram-negative bacteria.

Pfizer *World's largest producer of antibiotics*

PFIZER LTD · FOLKESTONE · KENT

* *Trade Mark of Chas. Pfizer & Co., Inc.*



PRELUDIN makes the task of the practitioner both simple and safe when dealing with cases of obesity. PRELUDIN is an appetite controlling agent which rapidly breaks the habit of overeating and enables the patient to adhere to a recommended diet without effort. Because it does not affect the heart or the blood pressure it is particularly suitable in cases of cardiovascular disorders or hypertension. PRELUDIN is supplied in 25 mg. tablets, in tubes of 20 or bottles of 250.

PRELUDIN* The appetite controlling agent that does not affect the heart

Brand of 2-phenyl-3-methyl-tetrahydro-1, 4-oxazine-hydrochloride

Manufactured and distributed in England by Pfizer Ltd., Folkestone, Kent, for
C. H. Boehringer Sohn, Ingelheim am Rhein
Registered proprietors of the Trade Mark *Regd. Trade Mark

Aspirin *and* Ulcer

"ASPIRIN is a serious gastric irritant, particularly in peptic ulcer patients."

"Calcium aspirin does not have this irritant action unless it has deteriorated through standing, and it can be used with impunity, especially if prescribed in soluble form. This simple measure would, in our opinion, cut down significantly the incidence of hæmatemesis and exacerbations of ulcer symptoms."

British Medical Journal, July 2nd 1955

SOLPRIN provides calcium aspirin in pure and stable form

CODIS is a compound tablet that provides codeine and phenacetin and calcium aspirin, in place of the ordinary aspirin in Tab. Codein. Co. B.P.

Neither SOLPRIN nor CODIS is advertised to the public

RECKITT & COLMAN LTD., HULL & LONDON (PHARMACEUTICAL DEPT., HULL)

NOW
you can have it in cartridges too!

Stabilised Injection of Dimycin, already available in 1 gm. and 5 gm. multi-dose vials (containing respectively 1 gm. Dimycin in 3 cc. and 5 gm. in 15 cc.), can now also be had in *1 gm. single-dose cartridges.*

This convenient form of Dimycin can be used in any commercially available syringe designed to hold disposable cartridges.

Stabilised Injection of DIMYCIN®

Equal parts of streptomycin and dihydrostreptomycin, stable for eighteen months.

GLAXO

Dimycin is also available in powder form: vials of 1 gm. and 5 gm.

GLAXO LABORATORIES LTD., GREENFORD, MIDDLESEX
BYRon 3434

• Trade mark

NEW

powerful bactericidal action against "frequent offenders"

Bactericidal against gram-positive and certain important gram-negative organisms, Albamycin has a range of activity which includes the following "frequent offenders": **staphylococci** (including "resistant" strains), **streptococci, pneumococci, proteus** and certain strains of **pseudomonas organisms.**

orally effective

*Albamycin**

(brand of novobiocin)

WELL TOLERATED

blood concentrations 10 to 50 times higher
than with other antibiotics + retention in the body
for as long as 24 hours = prompt clinical response
in many common infections *on 2 doses daily*

ADULTS — *500 mg. every 12 hours.*
CHILDREN — *15 mg./Kg. of body weight per day, usually in two* ***equal doses.***
SUPPLIED *250 mg. tablets, bottles of 16 and 100.*

* Trademark

Upjohn UPJOHN OF ENGLAND LTD · FLEMING WAY · CRAWLEY · SUSSEX

SUPPLIES OF THIS FOLDER ARE AVAILABLE FREE OF CHARGE

"Reducing Your Weight" is a new and easily followed guide to diet for weight reduction, and includes some simple advice and a varied menu. The folder is designed for handing to the patient, whose name may be written in a space provided on the cover.

Quantities of this folder are available free of charge to medical practitioners. For a supply, or a specimen copy, write to the Energen Dietary Service at the address below.

The Energen Dietary Service, staffed by qualified dietitians and under medical supervision, offers information and practical assistance in all dietary and nutritional problems. All services are free of charge, and practitioners are invited to apply for details.

(*Available in U.K. only*)

The Manager

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penicillin and sulphadimidine

the treatment of choice in

Pneumonia

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Eskacillin

200 Sulphа

a palatable liquid oral presentation in 1½ fl. oz. bottles

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ECSP66 (col.)

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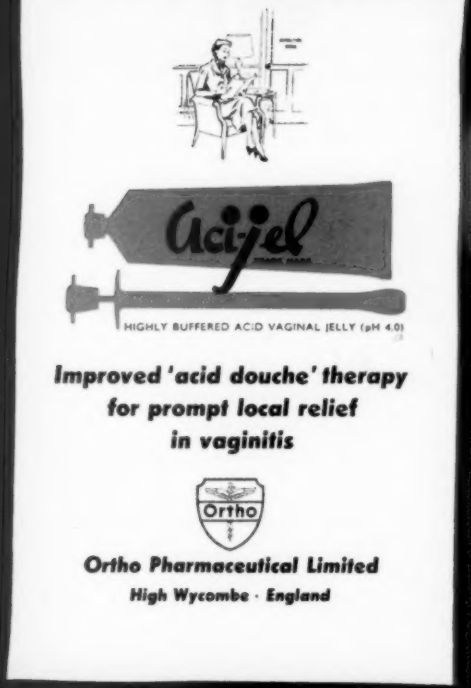


Aci-jel

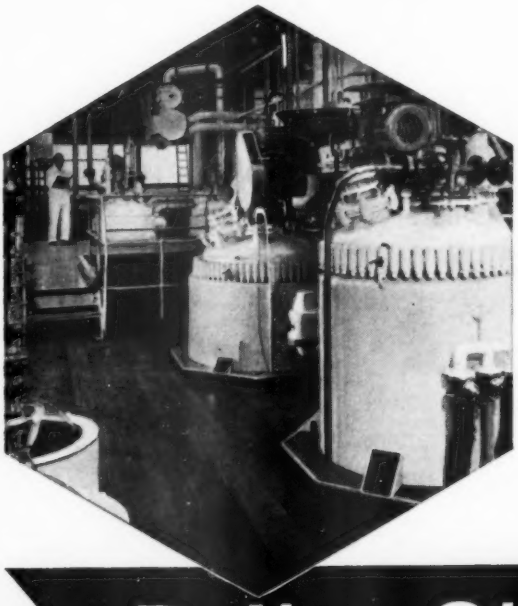
HIGHLY BUFFERED ACID VAGINAL JELLY (pH 4.0)

Improved 'acid douche' therapy for prompt local relief in vaginitis

Ortho

Ortho Pharmaceutical Limited

High Wycombe · England



Now freely available on prescription

Delta - Stab

Prednisolone

A synthetic steroid closely related to Cortisone and Hydrocortisone but offering the advantages of:—

- **improved therapeutic ratio**
- **fewer side-effects**
- **increased potency.**

Delta-Stab
is available as
SCORED TABLETS OF 1 & 5 MG.
CONTAINERS OF 30, 100 AND 500

Delta-Stab
like all other Boots corticosteroids, is entirely British made.

Literature and further information gladly sent on request

BOOTS PURE DRUG COMPANY LIMITED · NOTTINGHAM · ENGLAND

Boots

When fluid contents exceed requirements

DIAMOX*

*REGD. TRADE MARK

ACETAZOLAMIDE

Lederle

In conditions where excess fluid accumulates in body tissues, prompt, dispersal measures are called for. In such cases, by inhibiting carbonic anhydrase, DIAMOX acetazolamide produces prompt copious diuresis. It has proved its ability to control body-fluid balance in cardiac oedema, glaucoma and epilepsy. Published reports also show satisfactory results from DIAMOX in toxaemia and oedema of pregnancy, premenstrual tension, renal oedema, emphysema and drug-induced oedema. DIAMOX is a welcome departure from the mercurials and is well suited to long-term maintenance of ambulant and out-patient cases.

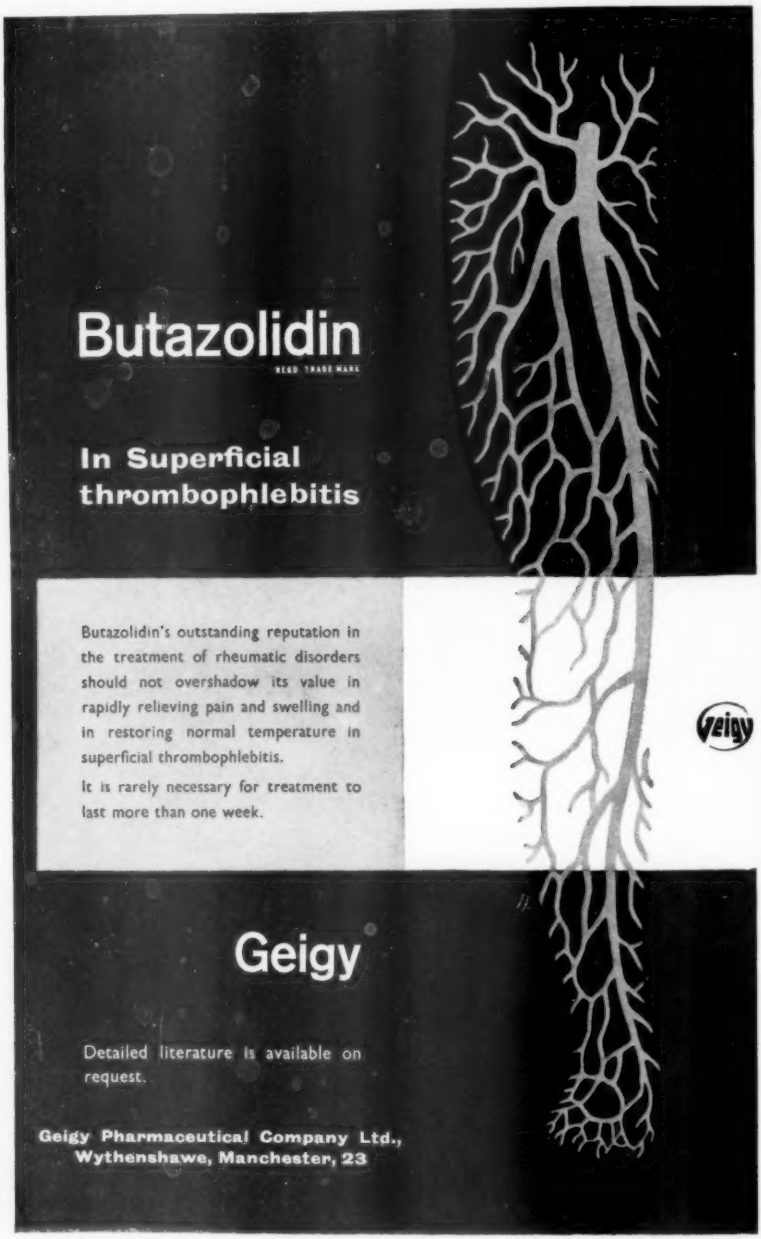
TABLETS of 250 mg.

BOTTLES of 25, 100 and 1,000

PARENTERAL Vials of 500 mg.

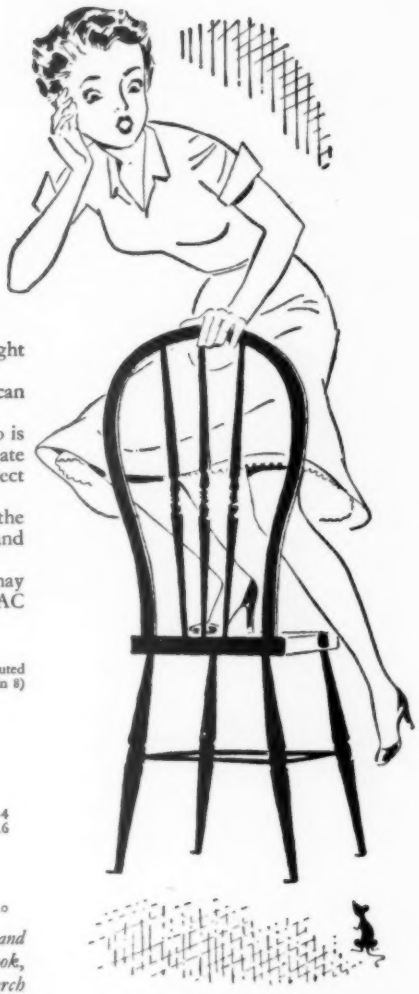
LEDERLE LABORATORIES DIVISION

Cyanamid OF GREAT BRITAIN LTD. London W.C.2


Butazolidin
REGD. TRADE MARK
In Superficial thrombophlebitis
Butazolidin's outstanding reputation in the treatment of rheumatic disorders should not overshadow its value in rapidly relieving pain and swelling and in restoring normal temperature in superficial thrombophlebitis.
It is rarely necessary for treatment to last more than one week.
Geigy
Detailed literature is available on request.
Geigy Pharmaceutical Company Ltd., Wythenshawe, Manchester, 23

PH.1338.

We are all Allergic to Something



This young lady to mice—you, perhaps to night calls in smoggy weather.
There is not very much that either of you can do to guard against this danger.
How much more fortunate is the baby who is allergic to milk protein! He has Cow & Gate Allergilac to step into the breach and to protect him from the cause of his trouble.
This special food has had practically all the lactalbumen and lactoglobulin removed and the casein rendered harmless.
When next you have a case of milk allergy, may we suggest that you give ALLERGILAC a trial?

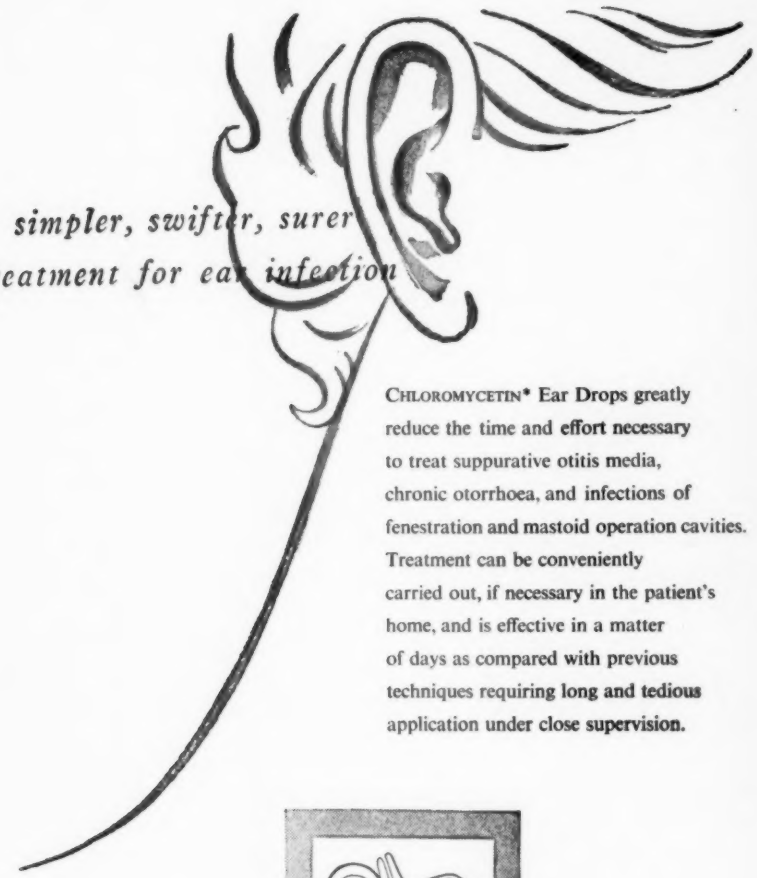
ANALYSIS

		Dry Food	Reconstituted Food (1 in 8)
Fat		16.0%	2.0%
Protein	Casein	25.8	3.2
	Lactalbumen	1.0	0.1
Lactose		43.4	5.4
Mineral Salts		8.0	1.0
Lactic Acid		2.8	0.4
Moisture		3.0	87.9
Calorific value	per oz.	123	15.4
	per 100 grms.	437	54.6
Calcium	per oz.	240 mgms.	
Phosphorus	per oz.	200 mgms.	
pH Value			6.0

Full details of all our products, with analyses and indications are given in our Medical Handbook, obtainable on request from the Medical & Research Department, Cow & Gate House, Guildford.
CLINICAL SAMPLES will also be sent.

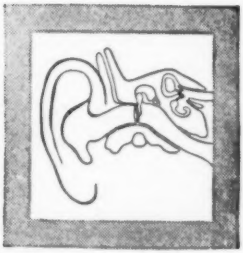
COW & GATE MILK FOODS

GUILDFORD SURREY 5480



simpler, swifter, surer
treatment for ear infection

CHLOROMYCETIN* Ear Drops greatly reduce the time and effort necessary to treat suppurative otitis media, chronic otorrhoea, and infections of fenestration and mastoid operation cavities. Treatment can be conveniently carried out, if necessary in the patient's home, and is effective in a matter of days as compared with previous techniques requiring long and tedious application under close supervision.



CHLOROMYCETIN *Trade Mark

EAR DROPS 10%

(Chloromycetin 10% in propylene glycol) in 5 c.c. vials with dropper, & bottles of 100 c.c.

Parke Davis
& Company Limited (Inc. U.S.A.)
HOUNSLOW, MIDDLESEX
Telephone Hounslow 2361
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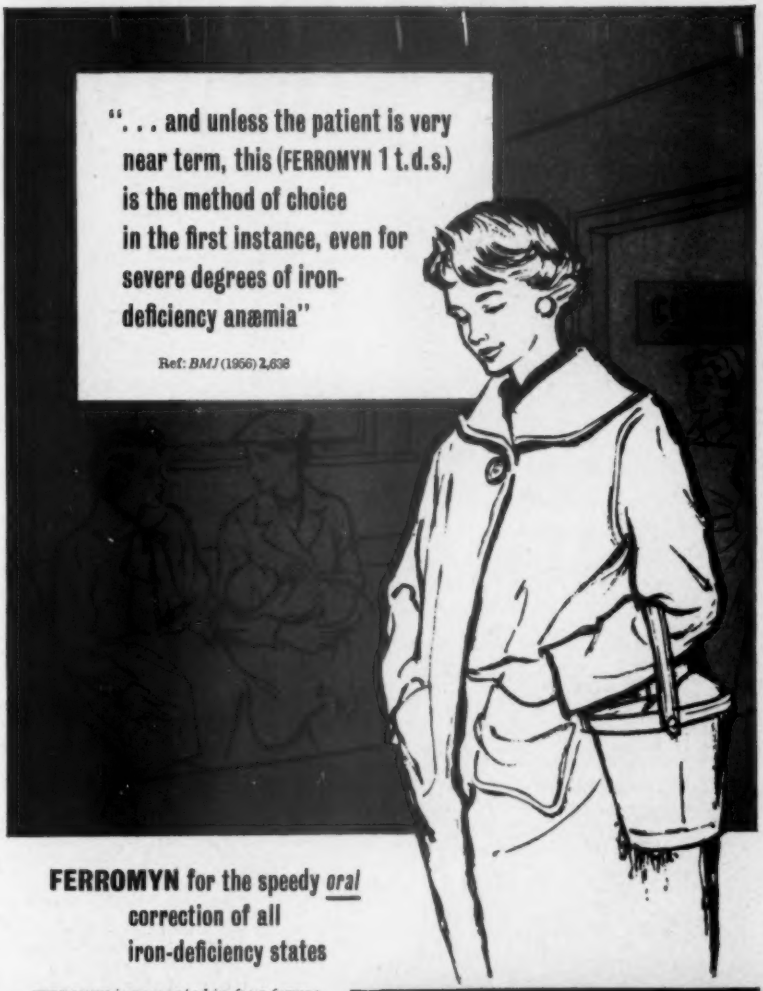
". . . and unless the patient is very near term, this (FERROMYN 1 t.d.s.) is the method of choice in the first instance, even for severe degrees of iron-deficiency anæmia"
Ref: BMJ (1956) 2,638

FERROMYN for the speedy *oral* correction of all iron-deficiency states

FERROMYN *is presented in four forms:*
FERROMYN TABLETS AND FERROMYN ELIXIR.
Each tablet/teaspoonful contains:
Ferrous Succinate 150 mg.
FERROMYN 'B' TABLETS AND ELIXIR FERROMYN 'B'.
Each tablet/teaspoonful contains:
Ferrous Succinate 150 mg. Aneurine Hydrochloride 1 mg. Riboflavin 1 mg. Nicotinamide 10 mg.

FERROMYN

CALMIC LIMITED, CREWE
Phone CREWE 3251-5

LONDON:
2 Mansfield St., W.1. Phone LANgham 8038-9

AUSTRALIA: 458-468 Wattle St., Ultimo, Sydney, N.S.W. **CANADA:** Terminal Building, York St., Toronto.

F5

The Ambulatory Treatment of Ulceration of the leg

The plaster used in the manufacture of "Lestreflex" is innocuous to newly formed tissue cells and leucocytes and the bandage is unsurpassed in the ambulatory treatment of ulceration of the leg. It provides a means of alleviating pain and promoting rapid healing. This bandage is often successful where allergy to other bandages has arisen.
"Lestreflex" is also available with strip ventilation, assuring aeration to the wound.

Write for booklet describing ambulatory treatment of ulceration of the leg.

LESTREFLEX
ELASTIC DIACHYLON BANDAGE
AVAILABLE ON E.C.10

DALMAS
WATERPROOF FIRST AID DRESSINGS

The Dalmas Doctor's Cabinet contains 180 waterproof dressings in eight sizes and shapes plus a one-yard spool of Dalmas Strapping.
Full details and samples available on request.

DALMAS
DALMAS LIMITED, LEICESTER & LONDON. Est. 1823
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For 40 years
"EUPINAL"
has been used successfully in the treatment of ASTHMA and CHRONIC BRONCHITIS and may be prescribed on N.H.S. Form E.C. 10

"Eupinal" contains Iodine and Caffeine combined in a most elegant and effective form.

In chronic Bronchitis "Eupinal" softens the tough accumulated mucus in the bronchial tubes and allows it to be more readily expectorated. In Asthma it possesses a more markedly soothing effect, lessening the frequency of attacks and reducing their severity and duration, and relieving breathlessness.

"Eupinal" contains no poison and is safe in use.

A PRODUCT OF
Cuxson, Gerrard & Co. Ltd.
OLDBURY BIRMINGHAM
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THE SAFEST AND BEST PREPARATION OF OPIUM

Nepenthe contains all the constituents of opium and has been prescribed for over 100 years. It has been found by generations of practitioners to be the best preparation of opium as it does not cause the unpleasant after-effects usually attributed to opiates. It can be given over a considerable period and the effect remains invariably constant.

Packed in 2-oz., 4-oz., 8-oz. and 16-oz. bottles and for injection in ½-oz. rubber-capped bottles, sterile, ready for use.

NEPENTHE Regd.
FERRIS & CO LTD
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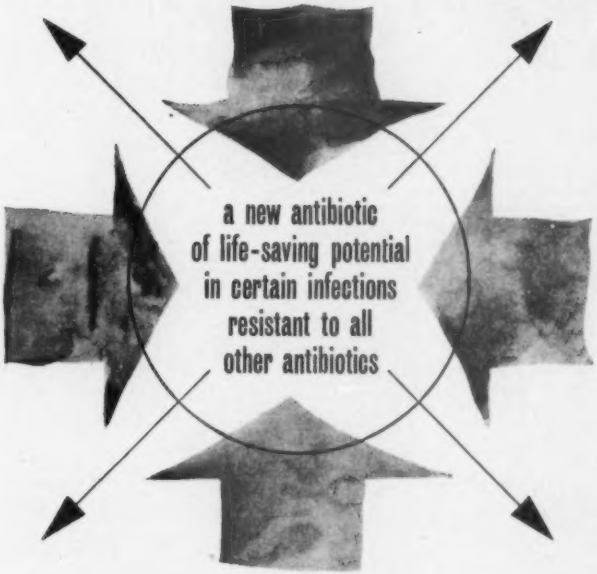

'CATHOMYCIN' is given orally and has proved to be highly effective in infections due to *Staphylococcus* and certain susceptible strains of *Proteus*, including those resistant to all other antibiotics.

HOW SUPPLIED: 'CATHOMYCIN' *Tablets are supplied in bottles of 16 and 100. Each tablet contains the equivalent of 250 mg. Sodium Novobiocin.*

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Excellent results have been reported in the following conditions:

Post-operative wound infections
Cellulitis
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Varicose ulcers
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Osteomyelitis
Infected amputation stump
Infected burns

'CATHOMYCIN'

TRADE MARK

(Sodium Novobiocin)

Available for prescription on Form E.C.10

MSD MERCK SHARP & DOHME LIMITED, HODDESDON, HERTS.

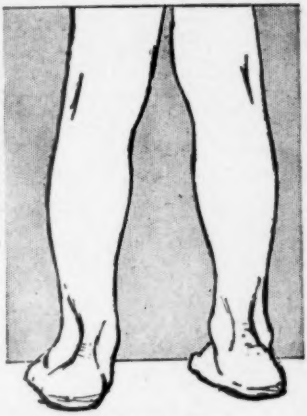
How do *YOU* tackle flat foot?

.. do you prescribe an external wedge on the shoes?

BUT the wedges soon wear away; and very often the child is made to feel self-conscious because his shoes look different from other children's.

Surely it's more logical to have a wedge *built-in* between the inner and outer sole—invisible, and completely unaffected by wear or repair of the shoe. That is how Start-rite INNERAZE shoes are made; why they are the only practical solution to this problem.

Information from Mr. W. J. Peake, James Southall & Co. Ltd., Crome Road, Norwich.



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Invisible Wedge Shoes by START-RITE

(who make the finest children's shoes of all types)

Inneraze Shoes are supplied only against medical prescription

ST. ANDREWS HOSPITAL, NORTHAMPTON

FOR NERVOUS AND MENTAL DISORDERS

President—THE EARL SPENCER

Medical Superintendent—THOMAS TENNENT, M.D., F.R.C.P., D.P.H., D.P.M.

This Registered Hospital is situated in 130 acres of park and pleasure grounds. Voluntary patients, who are suffering from incipient mental disorders, or who wish to prevent recurrent attacks of mental trouble; temporary patients, and certified patients of both sexes are received for treatment. Careful clinical, biochemical, bacteriological and pathological examinations. Private rooms with special nurses, male or female, in the Hospital or in one of the numerous villas in the grounds of the various branches can be provided.

WANTAGE HOUSE

This is a Reception Hospital in detached grounds with a separate entrance, to which patients can be admitted. It is equipped with all the apparatus for the complete investigation and treatment of Mental and Nervous Disorders by the most modern methods; insulin treatment is available for suitable cases. It contains special departments for hydrotherapy by various methods, including Turkish and Russian baths, the prolonged immersion bath, Vichy Douche, Scotch Douche, Electrical baths, Plombières treatment, &c. There is an Operating Theatre, a Dental Surgery, an X-Ray Room, an Ultra-Violet Apparatus, and a Department for Diathermy and High-Frequency treatment. It also contains Laboratories for biochemical, bacteriological, and pathological research. Psychotherapeutic treatment is employed when indicated.

MOULTON PARK

Two miles from the Main Hospital there are several branch establishments and villas situated in a park and farm of 650 acres. Milk, meat, fruit, and vegetables are supplied to the Hospital from the farm, gardens, and orchards of Moulton Park. Occupational therapy is a feature of this branch, and patients are given every facility for occupying themselves in farming, gardening, and fruit-growing.

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The seaside house of St. Andrews Hospital is beautifully situated in a Park of 330 acres, at Llanfairfechan amidst the finest scenery in North Wales. On the north-west side of the Estate a mile of sea coast forms the boundary. Patients may visit this branch for a short seaside change, or for longer periods. The Hospital has its own private bathing house on the seashore. There is trout fishing in the park.

At all the branches of the Hospital there are cricket grounds, football and hockey grounds, lawn tennis courts (grass and hard courts), croquet grounds, golf courses, and bowling greens. Ladies and gentlemen have their own gardens, and facilities are provided for handicrafts, such as carpentry, &c.

For terms and further particulars apply to the Medical Superintendent (Telephone: No. 4354, three lines Northampton), who can be seen in London by appointment.

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...On its own

* to strap a dislocated thumb. One-inch Elastoplast Plaster is used applied spica-fashion.

* to cover impetigo lesions, allowing undisturbed self-healing.

...Or to keep a dressing in place

* in cases where it is preferable to cut an individual strip rather than to use a ready-made first-aid dressing.

ELASTOPLAST PLASTER is flesh-coloured, made from light-weight cloth, and ideal for on-the-spot strapping and retention of dressings. It is far more comfortable and more efficient than a rigid plaster.

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1″ or 2″ x 1¾2 yds stretched and 1″ x 5/6 yds stretched

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plastic strapping 1″ x 1 yd and 1″ or 2″ x 3 yds

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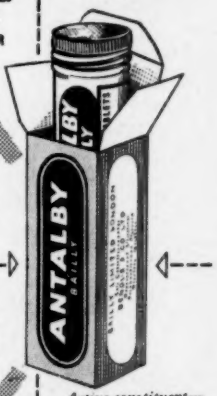
Advertised and Introduced ONLY to the Medical Profession



ANTALBY possesses a rapid and effective action in relief of spasm of the bronchial musculature and stimulates the respiratory centre.

INDICATIONS: Essential or symptomatic Asthma, Broncho-pulmonary or cardio-vascular dyspnœic affections. Dyspnœa of Emphysema.

PACKINGS	BASIC N.H.S. PRICES
Tablets: Tin of 30	3/5½ *plus* 1/- *P. Tax*
„ Dispensing pack: 250 tablets	24/- *plus* 7/2½ *P. Tax*
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Active constituent—Theophylline para-aminobenzoate of Piperazine

Sample and literature to the medical profession on request

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for effective treatment of...

chronic bronchitis, pulmonary congestion, asthma, and allied chest conditions.

cardiac failure, angina pectoris, Cheyne Stokes breathing, and other heart conditions.

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ORALLY · PER RECTUM · PARENTERALLY

ETOPHYLATE—soluble, neutral, stable theophylline ethanoate of piperazine—a powerful bronchodilator, cardiac and respiratory stimulant.

Tablets —250mg., for continuous, oral administration, without nausea or gastric irritation. Bottles of 25, 100, 500.

Suppositories —500mg., for prompt, prolonged action in both hospitalised and ambulant patients. Boxes of 12 and 144.

Ampoules —500mg. in 2 c.c., for painless intramuscular injections without discomfort. Boxes of 6 and 50.

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Etophylate is also available with Papaverine and Phenobarbitone

ETOPHYLATE is prescribable on the N.H.S.

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bring relief to cases of arthritis and rheumatism

In cases of soft-tissue rheumatism, and arthritic disorders, many doctors are tending more and more to regard Transvasin as an indispensable adjuvant to treatment.

For Transvasin is composed of the esters of nicotinic, salicylic and p-aminobenzoic acids. These esters readily pass the skin barrier in therapeutic quantities, and so enable an effective concentration of drugs to be built up where they are needed.*

Transvasin not only induces vasodilation of the skin with a superficial erythema, but also brings about a deep hyperaemia of the underlying tissues. It is non-irritant and can be safely used on delicate skins.

It is now being widely prescribed, with successful clinical results. Since a very small quantity is sufficient for each application, the cost of treatment is extremely low.

* *Therapeutische Umschau VIII, 1952, 10, 143.*

In 1 oz. tubes, basic N.H.S. price 2/6 plus P.T.

Salicylic acid tetrahydrofurfuryl-ester	*14%*
Nicotinic acid ethyl-ester	*2%*
Nicotinic acid n-hexyl-ester	*2%*
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ONE OF THE MOST
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SYNTHETIC
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HYDRO DELTALONE*

REGD. T.M.

is related to hydrocortisone as DELTALONE** *is to cortisone*

HYDRODELTALONE,
LIKE HYDROCORTISONE IS EFFECTIVE LOCALLY
AS WELL AS BY MOUTH.

HYDRODELTALONE IS
3 TO 5 TIMES MORE ACTIVE
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* *Brand of Prednisolone.*
** *Brand of Prednisone.*

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TABLETS

△ anti-inflammatory action 3 to 5 times that of cortisone or hydrocortisone.

△ gastro-duodenal side effects minimised by —protective coating of individual hormone crystals.

Presentation: bottles of 30 tablets of 1 mg. or 5 mg.

No purchase tax is applicable on Hydrodeltalone tablets.

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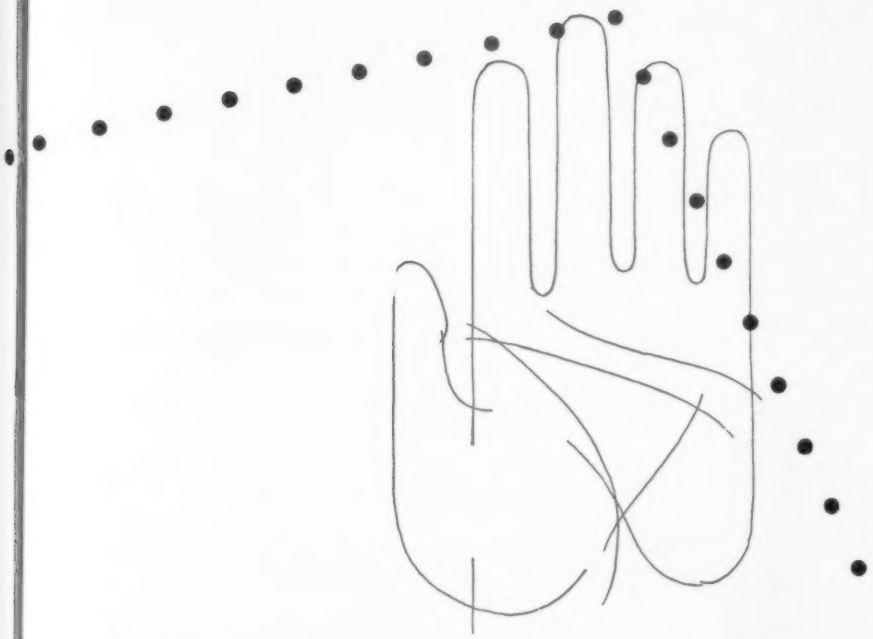
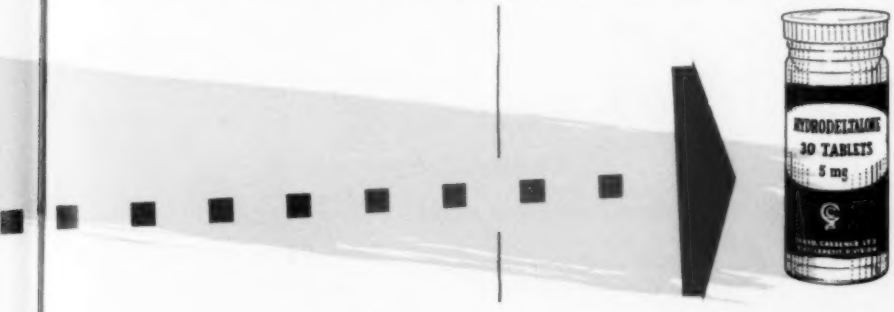


On local application, Hydrodeltalone has a rapid and powerful anti-inflammatory and anti-allergic effect.

In intra-articular and peri-articular injections, the anti-inflammatory effects of hydrocortisone are obtained with a smaller quantity of Hydrodeltalone.

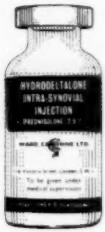


HYDRODELTALONE

intra-articular injections

for local articular and peri-articular inflammatory conditions

Presentation: 5 ml. vial containing 25 mg. of prednisolone acetate per ml. in saline suspension.



HYDRODELTALONE

skin ointment with neomycin

for infectious and non-infectious inflammatory and allergic disorders of the skin.

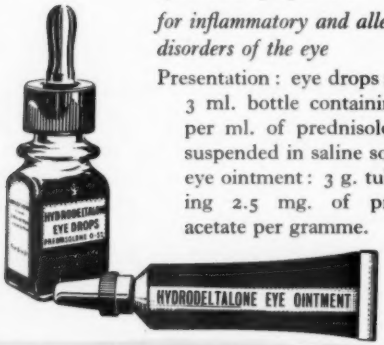
Presentation: tube containing 5 g. or 15 g.
Each gramme contains 5 mg. of prednisolone and 5 mg. of neomycin sulphate.

HYDRODELTALONE

ophthalmic preparation

for inflammatory and allergic disorders of the eye

Presentation: eye drops:
3 ml. bottle containing 2.5 mg. per ml. of prednisolone acetate suspended in saline solution.
eye ointment: 3 g. tube containing 2.5 mg. of prednisolone acetate per gramme.



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116 Victoria Street, S.W.1.

In atonic constipation

PURSENNID contains the pure Sennosides A & B of Senna Leaf in the form of their calcium salts.

PURSENNID, taken at bed-time, exerts a gentle but effective laxative action on the following morning.

PURSENNID does not cause griping, cramps or colic owing to the fact that the active compounds are pure glucosides, constant in quality and potency, and the preparation is free from irritant impurities contained in crude senna preparations.

PURSENNID

Bottles of 20, 40 and 200 tablets, each containing 12 mg.

SANDOZ

Schweiz. med. Wschr., 1941, **71**, 1093
Rev. méd. Suisse rom., 1941, **61**, 585
Amer. J. dig. Dis., 1945, **12**, 221

SANDOZ
PRODUCTS LIMITED

134, Wigmore Street, London, W.1

They like Lucozade..

and they can keep it down—

Lucozade has won its place in the sick-room because it is so very palatable. Not only this, when other food is refused or vomited, Lucozade is retained and quickly assimilated. And, so often, there is a happy turn for the better, well illustrated in this brief extract from a letter:

"My little boy was ill . . . and completely off his food . . . but he improved from the time of taking it."

(Signed) Mrs. V. Darlington, Birkdale.

LUCOZADE

the sparkling glucose drink

REPLACES LOST ENERGY

rovds M37/6

Ancestral habits...

When the Mediaeval King put aside his arms and stood alone, coldly footing it in chilly castle chamber, why the frowning concern with hair? Was it the scalp worry of all ages? Dandruff?

Sebaceous glands being the secretory things they are, there was then no royal remedy for the regal irritation. But today the old and familiar trouble has been mastered by SEBODERM, the Cetrimide Shampoo specifically for Dandruff.

Seboderm contains 15.6% of Cetrimide B.P., the quaternary ammonium prescribed as most effective against dandruff. Normally a single weekly treatment is sufficient to establish complete control.

Seboderm also contains 15.6% Cetyl Alcohol B.P. and 1% Lanolin, and as a finely emulsified, creamy shampoo it leaves the scalp free from irritation and the hair soft, silky and clean

Seboderm masters Dandruff

Professional sample will be gladly sent on request

PRIORY LABORATORIES LIMITED

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Zicthol and Pixcyl

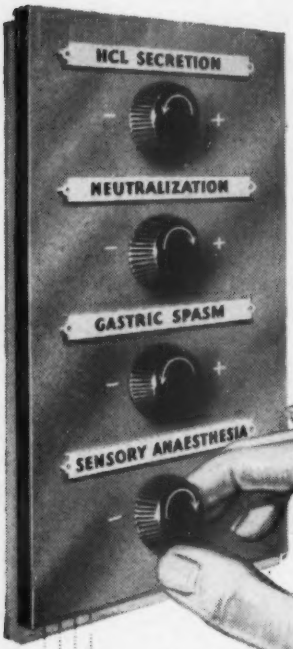
For each stage of Eczema-Dermatitis an appropriate treatment

In whatever phase Eczema-Dermatitis may present itself, there is a product in the Genatosan dermatological range to afford early relief and effective medication.

ACUDEX for the acute stage, **ZICTHOL** for the sub-acute and for infantile eczema, **ZICTHOL GREEN** for the secondary infected and **PIXCYL** for the chronic. Between them they provide the appropriate treatment for any of the numerous manifestations of the Eczema-Dermatitis group of lesions.

Available on E.C.10.

Genatosan Limited, Loughborough, Leicestershire



Fourfold Control

in Peptic Ulcer and Hyperchlorhydria

Packs and Prices to Pharmacists:

Bottle of 50
2/11 *plus* 10½*d. P.T.;*

Bottle of 250
12/6 *plus* 3/9 *P.T.;*

Bottle of 500
23/9 *plus* 7/1½ *P.T.*

ALOCOL COMPOUND is a new preparation formularized to provide comprehensive management of causal and symptomatic disturbances in the treatment of hyperchlorhydria and its manifestations, including gastric and duodenal ulcer.

Formula each Tablet

'Alocol' (Coll. Alumin. Hydroxide)...	11.58 gr.
Ext. Belladon. Sicc. B.P.	0.075 gr.
Papaverine Hydrochlor. B.P.	0.31 gr.
Benzocaine B.P.	0.31 gr.

ALOCOL COMPOUND tablets effect

.....	antacid protection
.....	diminished secretion
.....	reduced motility
.....	sensory anæsthesia

Alocol Compound thus provides the advantage of fourfold control—reduction of causal hyperacidic flow, and its neutralization; alleviation of symptomatic hypermotility and pain.

ALOCOL *Compound*

Professional sample on request from Medical Dept.

A. WANDER LIMITED, 42 Upper Grosvenor Street, London W.1.

M390

Ovaltine
in antenatal and postnatal care

THE INCREASED NUTRITIONAL DEMANDS arising during the latter half of pregnancy and the ensuing period of lactation, call for a general fortification of the patient's diet.

'Ovaltine' is eminently suitable as an aid in meeting this need because it provides concentrated nourishment in a palatable and easily assimilated form. It is acceptable to the most capricious appetite, such as often occurs in pregnancy.

'Ovaltine' possesses galactogogue properties. It also aids in maintaining the strength and general well-being of the nursing mother.

The high quality of its natural ingredients — malt, milk, cocoa, soya and eggs — its content of added vitamins, and the strictly hygienic conditions of its manufacture combine to provide a first-class nutritional product which has long enjoyed the approval of obstetricians.

OVALTINE

Vitamin Standardization per oz.—Vitamin B_1, 0.3 mg.; Vitamin D, 350 i.u.; Niacin, 2 mg.

A. WANDER LTD., 42 Upper Grosvenor St., Grosvenor Sq., London W.1.

Manufactory, Farms and 'Ovaltine' Research Laboratories: King's Langley, Herts.

M.379

'LANOXIN'

THE NEW NAME FOR THE ORIGINAL

DIGOXIN

When we discovered Digoxin in 1930 we used no other name to distinguish it. In those days, there was but one Digoxin—that issued by B. W. & Co. Today, it has become necessary to provide prescriber, pharmacist and patient throughout the world with that safeguard which a trade mark imposes . . .

THAT TRADE MARK IS 'LANOXIN'

NEW TITLE	'Tabloid' BRAND Digoxin *BECOMES* **'Lanoxin' BRAND Digoxin, B.P. (compressed)**
	Solution of Digoxin 'B. W. & Co.' *BECOMES* **'Lanoxin' BRAND Digoxin Oral Solution**
NEW PRODUCTS	**'Lanoxin' BRAND Injection** (for intramuscular or intravenous injection). *Boxes of* 6 × 2 *c.c. ampoules, each containing* 0·5 *mgm.*
	'Lanoxin' BRAND Digoxin Pædiatric Elixir *Bottles of* 2 *fl. oz., containing* 0·05 *mgm. per c.c.*
NO CHANGE OF TITLE	**'Wellcome' BRAND Injection of Digoxin**
	'Wellcome' BRAND Sterile Alcoholic Solution of Digoxin

N.B. Whenever oral Digoxin is ordered 'Lanoxin' may be dispensed

BURROUGHS WELLCOME & CO. (The Wellcome Foundation Ltd.) **LONDON**

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IT WAS RECENTLY reported (*Brit. med. J.*, 1: 444, 1957) that of 178 rheumatic patients, 25% could not take plain aspirin in adequate dosage.

Of this 25%, however, the great majority tolerated a modified aspirin such as Paynocil.

Not only are Paynocil tablets usually well tolerated by the stomach (even on the heavy dosage needed for rheumatoid arthritis), but they are extremely palatable, disintegrate instantly on the tongue without water, and cause no discomfort or unpleasant after-sensation.

...indicates PAYNOCIL

non-irritant, palatable, quick-dispersing aspirin

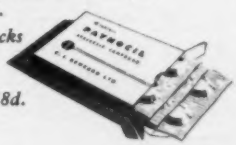
FOR ADULTS

PAYNOCIL

EACH TABLET CONTAINS

Acetylsalicylic acid ..... 10 grains
Aminoacetic acid ..... 5 grains

PACKAGES in sealed foil strips:
Cartons of 18.
Dispensing packs of 240: basic N.H.S. cost (tax free) 21/8d.



FOR CHILDREN

Junior PAYNOCIL

EACH TABLET CONTAINS

Acetylsalicylic acid ..... 2½ grains
Aminoacetic acid ..... 1½ grains

PACKAGES in sealed foil strips:
Cartons of 20.
Dispensing packs of 240: basic N.H.S. cost (tax free) 12/-.

Detailed recommendations for dosage in rheumatoid arthritis will be gladly supplied on request

C. L. BENCARD LTD. PARK ROYAL, LONDON, N.W.10

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DQV

The easily written, easily remembered contraction for

Acid-Stable ORAL Penicillin

'Distaquaine' V

trade mark

Crystalline penicillin V, free acid

DQV TABLETS	DQV ELIXIR	DQV SULPHA
Each tablet contains 60 mg. penicillin V. Bottles of 30, 200 and 1000	Each dose (½ fl.dr.) contains 30 mg. penicillin V. Bottles of 2 fl. oz. (30 doses)	Each tablet contains 60 mg. penicillin V. 0.30 gm. sulphadimidine 0.14 gm. sulphamerazine Bottles of 30, 200 and 1000

DOSAGE

Adults: 60 mg. or more every four hours
Children: Half the adult dose

Manufactured by

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THE PRACTITIONER

No. 1066 APRIL 1957 Volume 178

THE MONTH

The Symposium

It was only in 1948 that artificially produced radioactive isotopes became available for use in medicine in Great Britain. Today they are in use in every teaching hospital—and many others—in the country. This is the justification for devoting an entire symposium to the subject. Not that many doctors will ever handle radioactive isotopes personally, but it is essential that they should know something about them, and particularly about their use in therapy. For an intelligent understanding of their use a working knowledge is necessary of the principles involved, and to many doctors, particularly those of the older generations, the physics of radioactivity are wrapped in mystery. It is for this reason that we have introduced the symposium with three articles dealing, respectively, with the nature, the preparation, and the action of radioactive isotopes. These three articles, each written by a recognized authority on the subject, provide a simple straightforward account of the principles of radioactivity which should go far towards clarifying a highly complex subject. The following article on 'radioactive isotopes in research' indicates the tremendous potentialities of radioactive isotopes in the clarification of many outstanding biological problems.

The remainder of the symposium is devoted to the actual use of radioactive isotopes in clinical medicine. Perhaps most significant of these is that on 'a hospital radioactive unit'. The mere fact that such units now exist indicates the great advance that has been made in this field during the last decade. Equally significant is the inclusion of an article on 'radiography with radioactive isotopes' in the symposium. As the spectre of atomic warfare encircles the globe, it is with pride that Medicine and its associated sciences can note the progress that has been made in the harnessing of this new power to the service of humanity and the alleviation of suffering. We in this country can be particularly proud of the fact that, as pointed out by Dr. Seligman, 'Great Britain is by far the greatest isotope exporter in the world today'.

The American G.P.

In 1953-54, the University of North Carolina carried out an investigation of general practice in North Carolina. The results of this investigation, based upon the findings in 94 practices, have now been published in the December 1956 issue of the *Journal of Medical Education*. The report presents a picture of present-day practice in the United States which will be of interest to all practitioners in this country. At the same time it has many lessons for those concerned with the future of general practice in this country. The differences

between practice in our two countries are striking, but largely superficial. Perhaps the most striking difference is in the equipment considered necessary in the United States. Thus, 42.6 per cent. of the North Carolina practitioners owned an electrocardiograph, 42.6 per cent. an x-ray machine, and 35.1 per cent. a B.M.R. apparatus. The reading habits are also somewhat different: the average number of journals purchased per practitioner was 4.09; 17.2 per cent. of practitioners purchased five to six journals, whilst as many as 7.5 per cent. purchased seven to fifteen journals. The only two British journals included in the list are *The Lancet* and *The Practitioner*. In view of the once much-publicized criticism of standards of 'surgeries' in this country, it is of interest to note that in North Carolina 'considerable variation was noted in the appearance of these practitioners' offices. The majority were clean and attractive. Some, however, were only clean and neat and gave little evidence of thought for patient comfort. Almost a third of the offices visited might be properly considered as unacceptable for the use to which they were put'.

Perhaps the most important point of all in this report is the doubt thrown upon the value of postgraduate study unless carefully controlled. The collected evidence is taken to 'suggest that doctors who do more than sixty hours of postgraduate study annually may be doing more than is necessary for their purposes, or that interest in medicine or study may not be their primary motivation in attending medical meetings . . . It cannot be denied that postgraduate education may have a favourable effect on the doctor's practice but such an assumption could be held with greater certitude if increasing amounts of formal postgraduate education were accompanied by better performance'. Equally thought-provoking in these days of universal planning is the finding that 'there were physicians who had been good medical students and had received good training, who were not exceptional physicians. There were others whose performance as students was unusually poor, whose internships were of indifferent quality, who nevertheless became superior physicians'.

A Versatile Vaccinator

THE tale of 'Johnny Notions' is a salutary reminder that the shrewd acumen of our forefathers could produce results which compare most favourably with those obtained in these days of 'scientific medicine'. 'Johnny Notions', whose real name was John Williamson, was so-called by his neighbours because of his 'various attainments and superior talents'. According to his parish minister, he was 'a singular instance of an uncommon variety of talents, being a tailor, a joiner, a clock and watch mender, a blacksmith and a physician'. These laudatory comments are taken from the account of the united parishes of Mid and South Yell in the Shetland Islands contributed by the parish minister to the Old Statistical Account, 1792.

According to this account, which is quoted in the *Health Bulletin* (1957,

15, 2) issued by the chief medical officer of the Department of Health for Scotland, the population of these two parishes had increased considerably of late years, and one of the reasons given for this increase is 'the amazing success, with which inoculation has been attended. Formerly, the smallpox occasioned the most dreadful ravages in these islands; frequently carrying off a fifth part of the inhabitants. Now, hardly any suffer by this disorder'. The greater part of the credit for this is attributed to John Williamson. 'Unassisted by education, and unfettered by the rules of art, he stands unrivalled in this business. Several thousands have been inoculated by him and he has not lost a single patient'. Details are given of his technique. He insisted on 'the best matter', and kept it for seven to eight years before using it. To lessen its virulence he dried it in peat smoke and then buried it under ground, covered with camphor. Having made the inoculation, 'the only plaster he uses, for healing the wound, is a bit of cabbage leaf'. In the best tradition of Scottish medicine he was a therapeutic nihilist, and administered no medicines. It is claimed for him that 'it is particularly remarkable, that there is not a single instance in his practice, where the infection has not taken place, and made its appearance at the usual time'.

Amplified Auscultation and the Surgeon

'ROUTINE "broadcasting" of the surgical patient's heart' is recommended by G. D. Fish, Jr., and his colleagues (*Ann. Surg.*, 1956, **144**, 1013) as a simple, yet effective, means of giving immediate warning of cardiac arrest, or of impending arrest, to the anæsthetist. They give full details of the machine they have produced for this purpose and which they have now used in over a hundred cases. An ordinary diaphragm-type stethoscope head is attached to a pencil microphone by neoprene tubing. As the signal generated by the microphone is of the order of one-thousandth of a volt, it is perfectly safe under all conditions of operating-room use. Not only is the instrument easy to apply but in addition it is claimed that it 'is in no way an encumbrance either to the anæsthetist or the operating team'.

Many will probably question whether yet another 'gadget' in the overcrowded operating theatre is really necessary. On the other hand, in view of the increasing complexity of surgical operations, many of which can now be safely carried out on individuals who not so very long ago would have been considered 'bad risks', any reasonable means of helping to ensure that cardiac arrest is detected at the earliest possible moment is deserving of careful consideration. An incidental use of this new instrument is in the instruction of students and trainee surgeons in the importance of gentle handling of the anæsthetized patient. Rough handling of abdominal wounds, for instance, is 'reflected in the amplification of extraneous sounds superimposed on the normal heart sounds', whilst 'any pressure on the chest, as from an assistant's elbows while holding a retractor, is heard over the

loudspeaker'. May the time yet come when candidates for surgical appointments will be required to perform an operation while the selection committee listens in to the 'noises off' produced over the cardiac loudspeaker?

'Jug and Bottle'

THE modern pharmacy, with its chromium-plated dispensary approached through rows of elegantly packed proprietary preparations, is a very different place from the chemist's shop of the turn of the century, with its 'jug and bottle' trade. In a recent issue of the *Chemist and Druggist* (1957, **167**, 164) an octogenarian pharmacist recalls his memories of the period between 1890 and 1914. Household remedies then bulked large in the day-to-day business of the druggist: e.g. 'Four pennyworth each of oil of aniseed, oil of peppermint, laudanum, and paregoric, to be mixed with sugar syrup for a cough mixture'. Another common request was for '4 ounces of linseed oil'; this was for an infusion in which were dissolved 1 ounce of solazzi liquorice and 4 ounces of sugar candy for a cough mixture. The demand for ointments was not large, and those that were most popular have passed into the limbo of the past: 'trooper ointment' (for crab lice), 'white sipity' (for head lice), and basilicon (for drawing a boil). A favourite remedy for chilblains and chapped hands was camphor 'ice' or 'ball'. Penny boxes of pills were always in demand, and camphorated oil was so popular that it was made up in lots of 4 gallons at a time. 'Effervescent mag. cit.' was a ready seller in the summer—as a drink, not as a medicine. So long as it fizzed, and was tart and sweet, no questions were asked as to its constituents.

Cosmetics as known today were quite unknown, but there was a steady demand for perfume. A common request by the ladies on a Saturday night was 'sixpennyworth of perfume in a measure', from which it was promptly sprinkled by the lady on to her dress. Practically the only cosmetics sold were 'threepennyworth of carmine', *poudre de riz*, and peach bloom. Another popular request on Saturday nights was hair oil (olive oil and citronella), for which the customer brought his own bottle, and glycerin and rose water sold freely. Medicines and perfumes were by no means the only articles on sale in those days. For the dyeing of black dresses there was a regular demand for logwood chips (to make infusion for the dye) and green crystals (ferrous sulphate) for the mordant. Brunswick black was in demand every spring to 'revive the ubiquitous iron fireplace'. When red cabbage and onions were in season, a frequent order was 'a quart of vinegar and 4 ounces of mixed spices'. Occasionally there would be a request for 'essence of smoke' (pyroligenous acid) for giving a smoky flavour to a home-cured ham. Few pharmacists will regret the passing of the 'jug and bottle' trade, but the regimented citizen of the modern welfare state must be allowed to shed a tear for the passing of these old Dickensian days.

WHAT IS A RADIOACTIVE ISOTOPE?

By J. ROTBLAT, D.Sc.

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THE term isotope means 'the same place', and is used to denote those substances which occupy the same place in the periodic table of elements. The various elements which occur in nature are distinguished according to their chemical properties, and these can be simply explained by the structure of their atoms.

THE ATOM

Every atom consists of a central nucleus, and of a number of electrons revolving round it. This number of electrons is the main factor which determines the chemical properties of an element, because chemical reactions are due to an interchange of electrons between the atoms of the interacting elements. All the atoms of one chemical element have the same number of electrons, and this number, which is called the atomic number, defines the numerical place which the element occupies in the periodic table.

The atoms of a chemical element need not have the same structure; they may, for example, differ in weight. Since the weight of an atom has a negligible effect on chemical interactions, such atoms will behave chemically and biologically alike. The mass of the atom is concentrated in the nucleus and a difference in weight means a difference in the structure of the nucleus. The nuclei of atoms are made up of two types of particles, protons and neutrons (fig. 1), which have approximately the same weight but differ in their electrical properties, the proton has a positive charge—equal but opposite to that of the electron—whilst the neutron has no electrical charge. In every atom the number of protons in the nucleus is equal to the number of electrons revolving round it, i.e. to the atomic number. The total number of protons and neutrons is approximately equal to the atomic weight of the element, and is known as the mass number. Sodium, for example, which is element no. 11, has a mass number 23; this means that its nucleus contains 23 particles; since 11 of these are protons the remaining 12 are neutrons.

ISOTOPES

Atoms with the same number of protons but different number of neutrons will differ in weight but not in their chemical properties. Such atoms will, therefore, be isotopes of the same element.

Most chemical elements are a mixture of a number of isotopes. The isotopic composition of an element can be analysed by means of electrical

and magnetic fields, and in this way the number, weight and abundance of the isotopes can be determined. Some elements, usually those with an odd atomic number, like fluorine, sodium, phosphorus, or iodine, consist of one

CONSTITUENTS OF ATOM

		MASS (IN ATOMIC WEIGHT UNITS)	CHARGE
IN NUCLEUS	PROTONS	1	+
	NEUTRONS	1	0
IN OUTER ORBITS	ELECTRONS	$\frac{1}{1836}$	−

FIG. 1.—The constitution of an atom.

isotope only. Other elements may contain 2, 3 or even 10 isotopes. The total number of stable isotopes which occur in nature and which are distributed among the 81 stable elements is 274, an average of about 3.5 per element.

Since isotopes of the same element differ from each other in atomic weight, when describing an isotope one must state both the symbol of the element and the mass number. The latter is usually given as a superscript before the symbol, e.g. ^{31}P, ^{127}I, ^{16}O, ^{17}O, ^{18}O. From this notation (and assuming a knowledge of the periodic table of the elements) the constitution of the atoms can be immediately inferred. Thus, phosphorus, being the 15th element, has a nucleus containing 15 protons and 16 neutrons; iodine (atomic number 53) consists of 53 protons and 74 neutrons. All the three isotopes of oxygen (atomic number 8) have 8 protons in their nuclei, but the number of neutrons is 8, 9 and 10 respectively.

RADIOACTIVE ISOTOPES

The 274 isotopes referred to above are stable ones; this means that unless interfered with their nuclei remain unchanged for an infinitely long time. In addition to these, however, there exist in nature, or can be produced artificially, a number of isotopes which are unstable. The nuclei of such isotopes disintegrate spontaneously in the course of time. Such a disintegration usually produces only a small change in the structure of the nucleus, but as a result of this a new isotope is formed, and at the same time some radiation is emitted. Hence the name 'radioactive' applied to such isotopes.

The lack of stability of such isotopes follows from the composition of their nuclei. In order to confine the particles in the tiny space of the nucleus, the protons and the neutrons must act on each other with very strong attractive forces. On the other hand, the protons being positively charged repel each other. The outcome of this is that only for certain combinations of protons and neutrons is the resulting force such as to keep the nucleus

together. If the proportion of neutrons and protons is changed the repulsive force may predominate and the nucleus will tend to break up and change over into a stable form.

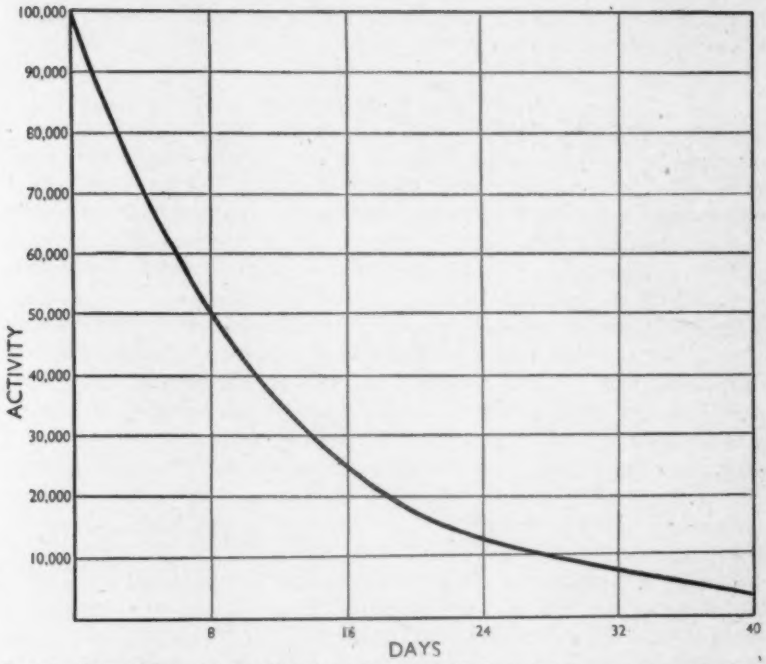

FIG. 2.—Rate of decay of a radioactive substance initially containing 100,000 radioactive atoms, and with a half-life of 8 days.

The break-up of a radioactive nucleus does not take place instantaneously. In a given radioactive substance some nuclei break up in a very short time, but others may exist for a very long time. It is a process governed by chance, but if the substance contains a very large number of unstable atoms a simple statistical law is observed, namely, that the same fraction of all the radioactive atoms present in the substance breaks up in equal intervals of time. The quantity which is usually employed to characterize the rate of decay is the so-called half-life, the period of time in which half of the radioactive atoms in the substance decay. If we consider, for example, a substance with a half-life of 8 days and containing initially 100,000 radioactive atoms, then after 8 days 50,000 atoms will be left; after 16 days 25,000; after 24 days 12,500, and so on. The graph in fig. 2 shows the rate of decay of such a substance as a function of time.

Since a radioactive substance is detected by the radiations emitted, and this depends upon the number of atoms breaking up, it is usual to measure

the strength of a radioactive substance in terms of the number of disintegrations per second, or activity. The unit of activity is called the curie; it is nearly the activity of 1 gramme of radium and is equal to the quantity of a radioactive substance in which 37,000 million nuclei break up every second. In practice smaller units are employed, i.e. the millicurie (one-thousandth of a curie) and the microcurie (one-millionth of a curie).

α-, β-, AND γ-RAYS

In most cases the break-up of an unstable nucleus consists of a change of a neutron into a proton, or vice versa. These two particles may be considered to be different states of the same particle of matter. The actual process of transformation is complicated and not yet well understood, but it is known that eventually it leads to the production of an electron. Thus, when a neutron changes into a proton, an electron is produced and is immediately emitted from the nucleus. If a proton is transformed into a neutron an electron with a positive charge, a positron, is produced and emitted. The emission of electrons, or β-rays, as they are called, can be detected by means of various instruments, and it is through the observation of such radiation that radioactivity is measured. β-rays are usually emitted from an unstable nucleus with some energy and since they have a very small mass, they start off with a great velocity which enables them to penetrate through some thickness of matter: i.e. a few millimetres of tissue. The energy of nuclear radiations is measured in units of million electron volts (MeV); the higher the energy the greater the penetration.

Not all of the energy available in an unstable nucleus is taken up by the emitted particles. Often some energy is left over and is subsequently emitted in the form of a pure radiation, identical in nature with x-rays. These radiations are called γ-rays and are much more penetrating than β-rays; they can pass through many centimetres of tissue.

In the heaviest elements yet another mode of decay, by the emission of α-particles, is observed. α-particles are nuclei of atoms of helium. Being much heavier than β-rays they can penetrate only through a very small thickness; a thin sheet of paper will stop them completely.

As in the case of stable isotopes each radioactive isotope is denoted by its atomic number and mass number; in addition, however, they are characterized by their half-life, type of emitted radiation and its energy.

The phenomenon of radioactivity was first discovered in the heaviest elements which occur in nature: e.g. uranium, thorium, radium. Later, however, it became possible to transform ordinary atoms into radioactive ones. This can be done either by the use of atom-smashing machines, in which charged particles are accelerated to very high energies and then employed to bombard and break up nuclei; or by means of nuclear reactors in which neutrons are used in a similar way. In addition, the complete break-up, or fission, of uranium nuclei leads to the production of a large number of radioactive isotopes.

Altogether, it has now been possible to produce over 800 radioactive isotopes, about three times more than the number of stable isotopes. There is now at least one radioactive isotope of every chemical element.

THE SIGNIFICANCE OF RADIOACTIVE ISOTOPES IN MEDICINE

The great importance of radioactive isotopes for medical and biological work arises from the fact that the radioactive isotope is chemically and biologically identical with the stable isotope, but the possession of radioactivity labels it, making possible its detection by observing the radiations

Isotope	Symbol	Half-life	Radiations emitted	Energy of β-rays (MeV)	Energy of γ-rays (MeV)
Tritium	^{3}T	12.26 years	β	0.0176	—
Carbon-14	^{14}C	5,900 years	β	0.155	—
Sodium-24	^{24}Na	15.06 hours	β, γ	1.400	1.38, 2.75
Phosphorus-32	^{32}P	14.30 days	β	1.711	—
Sulphur-35	^{35}S	87.1 days	β	0.167	—
Potassium-42	^{42}K	12.5 hours	β, γ	3.54	1.53
Calcium-45	^{45}Ca	164 days	β	0.25	—
Chromium-51	^{51}Cr	27.8 days	γ	—	0.325
Iron-59	^{59}Fe	45 days	β, γ	0.46	1.1, 1.3
Cobalt-60	^{60}Co	5.27 years	β, γ	0.306	1.17, 1.33
Arsenic-76	^{76}As	26.5 hours	β, γ	2.97	0.55—2.05
Bromine-82	^{82}Br	35.7 hours	β, γ	0.46	0.5—1.5
Rubidium-86	^{86}Rb	18.6 days	β, γ	1.79	0.53, 1.08
Strontium-90	^{90}Sr	27.7 years	β	0.61	—
Yttrium-90	^{90}Y	64.8 hours	β	2.26	—
Ruthenium-106	^{106}Ru	1.0 year	β	0.04	—
Iodine-131	^{131}I	8.05 days	β, γ	0.61	0.28, 0.36
Xenon-133	^{133}Xe	5.27 days	β, γ	0.34	0.081
Cæsium-137	^{137}Cs	30 years	β, γ	0.52	0.67
Cerium-144	^{144}Ce	290 days	β, γ	0.327	0.03—0.14
Thulium-170	^{170}Tm	127 days	β γ	0.95	0.084
Tantalum-182	^{182}Ta	111 days	β, γ	0.51	0.07—1.22
Gold-198	^{198}Au	2.70 days	β, γ	0.96	0.41

TABLE I.—Some radioactive isotopes used in medicine and biology.

emitted. The sensitivity of detecting instruments, such as the Geiger counter or scintillation counter, is so great that it is possible to detect by these means a quantity of matter millions of times smaller than that detectable by any other method.

For medical purposes, only a small fraction of all the radioactive isotopes can be used, since the suitability of an isotope depends upon its half-life, energy emitted, availability, and specific activity, as well as its biological properties. A list of isotopes most frequently used in medical and biological work is given in table I.

THE PREPARATION OF RADIOACTIVE ISOTOPES

By HENRY SELIGMAN, Ph.D.
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Any atom consists of a nucleus surrounded by electrons. The electrical charge of a nucleus of an atom defines the chemical element and the mass of the nucleus defines the isotope. Therefore if, for example, one has 79

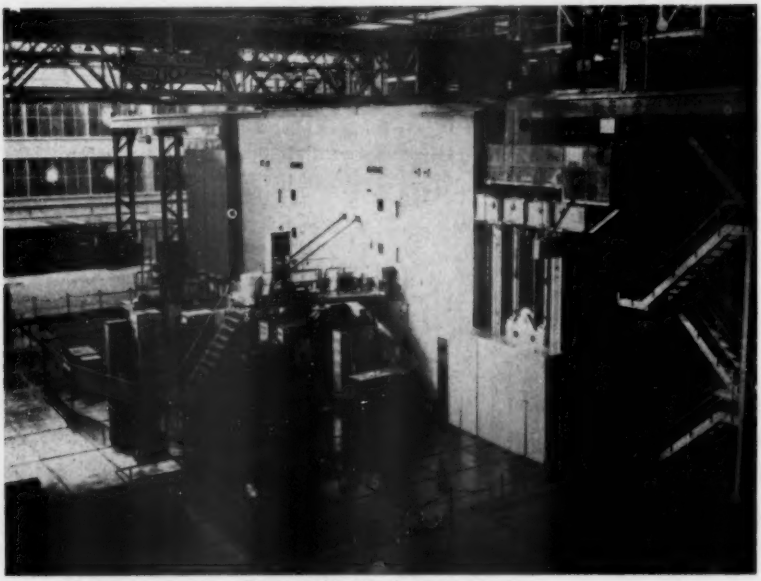

Fig. 1.—An atomic reactor.

electrical charges of a nucleus, the element is gold. The gold atom can have a weight of 197—this is the stable isotope of gold; but it can have different weights varying from 187 to 203, and all the other isotopes except the one with the weight of 197 are unstable—they are radioactive, which means that they emit radiations.

THE RATIONALE

To make a new isotope it is therefore necessary to change the weight of the nucleus; if, as a result of this change, a non-stable nucleus is obtained, this means that a radioactive variant has been formed. In other words, to make radioactive isotopes it is necessary to change the weight of normal stable nuclei. This can be done by bombardment of atoms with particles.

They can be particles carrying electric charges, like protons or deuterons, or they can be neutral particles like the neutrons which are the unit of mass. The latter particle is especially suitable for bombardment as, because of its electrical neutrality, it can penetrate more easily into the nucleus. All that is necessary therefore is to bombard nuclei with particles which have a high enough energy to penetrate into the nucleus.

This can be done by producing, for example, protons or deuterons and bringing them to a high enough speed in a cyclotron or a similar machine, or it can be done by using atomic reactors (fig. 1) where we have a vast amount of neutrons which result from the fission, or splitting, of uranium.

FIG. 2.—Placing small aluminium cans, containing target material, in an atomic reactor.

CYCLOTRON OR ATOMIC REACTOR

In a cyclotron, only one species of radioisotope can be made at a time and this is rather expensive, whilst in an atomic reactor many hundreds, or even thousands, of species of radioisotopes can be produced at the same time, but there is a fundamental difference between cyclotron- and reactor- produced radioactive materials. Electrically charged particles, as used in cyclotrons and incorporated into the nucleus, always change the target element. Neutron bombardment, however, as done in an atomic reactor, normally does not necessarily change the target element.

If we have, for example, gold which is stable gold with the weight of 197, and it undergoes bombardment with neutrons in a reactor, we shall obtain gold with one unit heavier as a result, which is gold-198. Written in a physicist's language:—

$$\text{Au } 197 + \text{n} = \text{Au } 198 + \gamma$$

or (shorter) Au 197 (n, γ) Au 198

There are many exceptions, where a neutron bombardment can change an element; this will always happen when an electrically charged particle is thrown out of the nucleus. One such example is the production of radioactive phosphorus from sulphur:—

$$^{32}\text{S} + \text{n} = {}^{32}\text{P} + \text{p}$$

There is still a number of isotopes which are made more easily with an electric machine. For example, the long-lived sodium-22 can be much more conveniently produced in a cyclotron, whilst the short-lived sodium-24 is best produced in an atomic reactor, but the reactor-produced materials are generally much cheaper. It is therefore not surprising that more than 99 per cent. of the shipments of radioactive materials going out are radio-

active materials produced exclusively in atomic reactors. For this reason, only atomic-reactor-produced isotopes will be discussed in this article.

THE TECHNIQUE

In order to make an irradiation we have to choose first the proper target material. Usually this is not a compound or a big molecule because the radiation itself is destroying chemical bonds and decomposing materials. For this reason chemically simple target materials are usually used. These may be pure metals or oxides of metals, but there are exceptions to this rule.

The irradiation time depends upon a number of physical data: e.g. the half-life, the cross-section and the neutron flux.

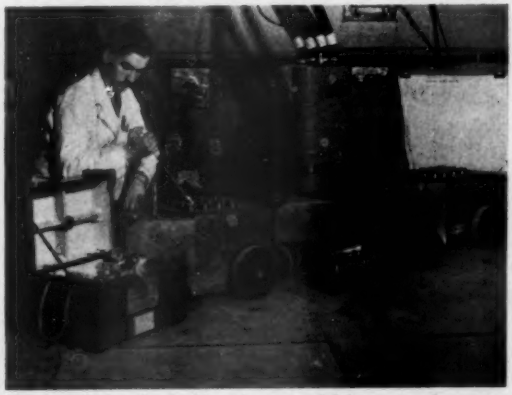

FIG. 3.—Removing radioactive material from atomic reactor by remote control.

The place in the reactor where the irradiation should take place has to be decided. This place varies according to the speed of neutrons desired, as in many cases the reactions are influenced by this. For example, sulphur in a slow neutron flux will give radioactive sulphur but the same element bombarded by fast neutrons will give radioactive phosphorus. Also some material which may be influenced by high temperatures will have to be put in a specially low neutron flux where the temperatures are usually lower or special cooling arrangements will have to be made.

The target materials have to be weighed and are usually put into small aluminium cans which are then inserted into an atomic reactor. This can be done even while the pile is running (fig. 2). After a certain time this material is removed by remote control (fig. 3) and transferred to the handling bay. Here the radioactivity is checked for its strength and the material is then loaded into transport containers. Some materials can then be used directly and are shipped from Harwell. These are, for example, radioactive sodium in the form of a salt; cobalt in the form of wire, or little cylinders; or gold in the form of grains for insertion into tissue.

CHEMICAL PROCESSING

Most materials, however, have to be chemically processed. Sometimes the radioisotope has to be separated; it has to be put into another chemical compound, standardized and often sterilized. Practically all chemical work of this nature is done by the Radiochemical Centre at Amersham which is a part of the Atomic Energy Research Establishment. The Radiochemical

Centre receives irradiated material from Harwell for chemical processing; the most important medical isotopes prepared at Amersham are iodine-132 which is prepared either by extraction from fission products or, as in the case at Amersham, by separation from a parent which is radioactive tellurium-132 (fig. 4). Another one is phosphorus-32 which has to be chemically separated from irradiated sulphur. After these chemical separations have been done by remote control the activity of the solutions has to be assessed and they have to be checked chemically and eventually the material has to be dispensed (fig. 5) and some of it has to be sterilized afterwards. Radioactive materials, such as iodine or phosphorus, which are separated chemically from other elements, are usually designated carrier-free, which means that practically all the atoms of the material are radioactive—a fact which can never be quite achieved practically. These materials have therefore a very high specific activity (activity per gramme): an extremely important factor in quite a number of applications.

FIG. 4.—Operating a plant for the extraction of iodine-131.

FIG. 5.—The dispensary at the Radiochemical Centre, Amersham, for beta-emitting isotopes.

MEDICAL RADIOACTIVE ISOTOPES

Many additional preparations of radioactive materials are made for the medical profession. For example, chromium-51 or iron-59 produced in the right form is used for certain blood determinations. Colloidal gold and gold

in the form of grains are used for malignant disease. A number of active materials whose radiations are not very penetrating, beta-active materials, are produced in special forms, some of them for ophthalmic applications (fig. 6), others for surface treatment of lesions. Radioactive materials such as phosphorus-32, strontium-90, cerium-144 and ruthenium-106 are being used in special applicators where the material may be put into certain plastics or into metal foil in order to make its use safe. It is always an important fact, which has to be verified, that material which is to be used from the outside is so safe that no loose radioactivity can come into the body and this is achieved by incorporating the radioactive material safely into plastics or metal foils. For biochemical work many organic compounds have been synthesized at the Radiochemical Centre; these are generally used as tracers.

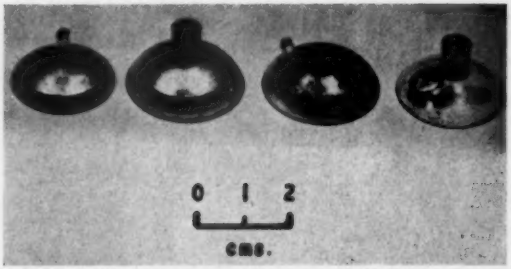

FIG. 6.—Method of supplying radioactive isotopes for ophthalmic use.

More recently very big sources of radioactive materials have been produced and are being used in therapy in this country. For example, large sources of cobalt-60 produced in atomic reactors are being used for teletherapy treatment, and only a few months ago the first teletherapy source made from atomic fission products (waste products) was prepared in this country by the Industrial Group of the Atomic Energy Authority. In this case radioactive cæsium-137 had been isolated from used atomic fuel rods. It is hoped that in the future this material will become available in bigger quantities and that many more hospitals will be able to obtain such a source.

CONCLUSION

In Great Britain we have the closely coordinated services between the Isotope Division at Harwell, the Radiochemical Centre at Amersham, and the Windscale Works of the Industrial Group, all belonging to the Atomic Energy Authority, and we are in the happy position to have available in this country a greater variety of radioactive materials than anywhere else in the world. Constantly we add to our lists new radioactive materials or old ones but in different form. It is not surprising therefore that Great Britain is by far the greatest isotope exporter in the world today, some fifty countries obtaining their isotopes from this country.

THE ACTION OF RADIOACTIVE ISOTOPES

By J. F. LOUTIT, D.M., F.R.C.P.
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RADIOACTIVE atoms may be encountered clinically within the body in three different connexions: in diagnosis, in therapy and in occupational medicine.

EMISSIONS FROM RADIOACTIVE ATOMS

The unstable radioactive atom disintegrates and emits some form of radiation in the attempt of the atomic nucleus to stabilize itself. Many of the naturally radioactive elements of high atomic number (such as uranium, thorium, radium) emit α-particles, nuclei of helium atoms. Others, and many of the artificially produced radioactive isotopes of stable elements, give off β-particles. In either case (α- or β-particle-emission) an electromagnetic radiation—a γ-ray—may be associated with the particle. These radiations, particulate and electromagnetic, have this in common: they cause ionization within the material in which they are absorbed—air, water or tissue. They are thus classed among the ionizing radiations and are to be differentiated from visible and ultra-violet light and other non-ionizing radiations.

The α-particle, a massive thing comparatively speaking and having a positive electric charge, cannot travel far. Its path is limited to 12 inches (30.5 cm.) or so in air and to a few tens of microns in water or tissue. As it expends its kinetic energy it causes densely packed ionizations along its short path. The β-particle, an electron, is several thousand times less massive and travels farther, up to a centimetre in tissue; but the ionizations along its path are relatively scanty until near the end of its track. γ-radiation can be considered as similar in many ways to particulate radiation, each quantum on absorption in a medium leads to the ejection of an electron from the molecule in which it is absorbed. It differs in that it is much more penetrating and even soft γ-rays and the physically similar x-rays can travel long distances in tissue before giving up their energy, whilst hard highly energetic γ-rays can penetrate right through the body.

TRACER STUDIES FOR DIAGNOSIS

In diagnosis one makes use of the fact of the disintegration, and the liberated energy—particulate or electromagnetic—is picked up by an appropriate device: e.g. ion chamber, Geiger counter, scintillation counter. One can thus determine such parameters as circulation times, efficacy of uptake and utilization of elements and radicals by the so-called 'tracer method'. It is particularly important that the radioactive material should be present in no

more than the trace or minimal amount necessary for the exercise. Even in chemical reactions *in vitro* too great a concentration of radioactivity can alter the properties of reactants. Biological systems *in vivo* are still more sensitive so that misuse of radioactivity is not only misleading but dangerous.

PHYSICAL AND PHYSICOCHEMICAL EFFECTS OF IONIZATION

Under suitable conditions this damaging action can be utilized for therapeutic purposes. The damage is due to the process of ionization with probably additional effect from molecular excitation such as occurs under the influence of ultra-violet radiation. The ionization may act by direct or indirect effect. The direct action is thought to be mainly on large protein molecules which, when electrons are ejected, undergo internal rearrangement and are denatured as a consequence. If they are essential proteins and not replaceable, as may be the case with certain nuclear materials (e.g. a gene controlling a cytoplasmic enzyme), the cell is seriously embarrassed. The indirect action is probably mainly through the ionization of the water molecule—the most abundant molecule in tissue. Several reactions are known to occur:—

$$(1)\ (a)\ H_2O \rightarrow H_2O^+ + e^-$$
$$\quad\ (b)\ H_2O^+ \rightleftharpoons H^+ + OH$$
$$(2)\ (a)\ e^- + H_2O \rightarrow H_2O^-$$
$$\quad\ (b)\ H_2O^- \rightleftharpoons H + OH^-$$
$$(3)\ (a)\ H + O_2 \rightarrow HO_2$$
$$\quad\ (b)\ 2HO_2 \rightarrow H_2O_2 + O_2$$

The positively charged water molecule left when an electron is ejected under the influence of radiation dissociates to give the normal hydrogen ion and the abnormal hydroxyl radical. This latter is a highly active oxidizing agent. The hydrogen radical formed in equation (2) is equally a highly active reducing agent but in the presence of molecular oxygen can form oxidizing substances as in equation (3). These reactions of oxidation or reduction, occurring focally in cells, in chromosomes or other sensitive targets, could also cause irreparable damage.

These reactions, direct or indirect, will occur in the immediate environment of the ionization or at variable distances from the radioactive atom, depending upon which particular isotope it is of which particular atom. An α-emitting isotope of, say, radium will have this extremely dense ionization in a track of some 30μ from the disintegrating atom. The damaging effect resulting from this concentration of ionization is about ten times greater per unit of energy delivered per unit mass (i.e. physical dose) than with β-radiation. Whilst β-particles and x- and γ-rays have about the same biological efficiency for equal physical dose, the greater range of the γ-rays leads to the physical energy being distributed more widely than with β-rays.

BIOLOGICAL FACTORS OF LOCALIZATION

In addition to these physical factors one has to consider the biological factor of localization of a particular atom. Radioactive sodium (^{24}Na for

instance) would be expected to distribute itself within the body uniformly in extra-cellular water. Practically all of the β-rays of this particular nucleide would be effective in giving whole-body-irradiation. The γ-rays, however, though coming from the same uniformly distributed atoms, would be lost to a considerable extent outside the body. Radioactive iodine, ^{131}I, is also a $\beta+\gamma$ emitter, but the iodine is highly concentrated in the thyroid, so that the β-rays there give an intense irradiation and the γ-rays a more widely distributed less intense dose. Where high biological concentration is combined with high biological effectiveness (α-rays), then one gets the maximum of local effect.

UTILIZATION OF IONIZATION FOR THERAPY

Only in a few instances has biological concentration been suitable for therapeutic purposes. Iodine and the thyroid is the most impressive instance. Phosphate and actively dividing cells utilizing phosphate for desoxyribosenucleic acid formation, e.g. the bone marrow in polycythæmia vera, is another.

OCCUPATIONAL HAZARDS

A few occupations in the past were concerned with the mining, processing or use of the naturally radioactive materials. Already there is an important chapter in the history of industrial medicine dealing with the attendant disorders from the intake of these substances into the body. Inhalation of radioactive ores has led, when the exposure was long, as in the Schneeberg and Joachimstal mines, to carcinoma of the lung. Ingestion of radium, mesothorium, and radiothorium by those who first refined these materials or used them in the luminizing industry has now long been known to cause, depending upon dose, subacute refractory or aplastic anæmia, necrosis of bone and osteosarcoma. As a consequence of these earlier mistakes it has been possible to assess the risks at the present day and in future occupations involving the production and use of artificially produced radioactive materials.

PATHOLOGICAL ASPECTS

From the foregoing it can be concluded what is the pathological effect of excess irradiation. It is necessary to stress that we can only be certain about the effects of the excess. There is in all circumstances natural irradiation of the body both from without and within. The earth itself contains everywhere traces of the naturally radioactive materials, uranium and thorium and their decay products. In some geological formations, especially in areas of granitic rock, the concentration may be several times that of the terrestrial average. In a few restricted localities the concentration may be high enough to make mining profitable. Other naturally radioactive materials are potassium and carbon. Each of these elements, which are essential constituents of tissue, has a radioactive isotope, ^{40}K and ^{14}C respectively, which is present in minute amount together with the more abundant stable isotopes, ^{39}K, ^{41}K, ^{12}C and ^{13}C. Moreover, we receive

irradiation from cosmic sources. How far these radiations are with or without effect on living tissue is at the moment still a matter of speculation.

If we consider the effect of excess radiation we deduce from the introduction that irradiation can lead to death, either of individual cells or tissue or the whole organism. Some tissues are much more vulnerable than others. As a general law it can be said that tissues in a constant state of reproduction are those which are radiosensitive. Thus hæmopoietic tissue, both bone marrow and lymphatic tissue, is readily destroyed; the mucosa of the gut is if anything even more sensitive and so is the male germinal epithelium, whilst skin is rather less affected. In fact the biological process which apparently is most vulnerable is that of cell reproduction. Mitotic division is the method by which this is generally considered to occur, so that much research has been devoted to the investigation of the effects of radiation thereon. Nevertheless, interference with mitosis should not be rated as the sole cause of death of cells. The small lymphocyte is usually thought to be an end-cell and not to undergo mitotic division, yet it is extremely radiosensitive. Following irradiation its nucleus rapidly becomes pyknotic and cytolysis supervenes. Presumably the radiosensitive ovum dies in similar fashion. This process of cell death without division can be seen to occur in other tissues where cell division by mitosis is actively going on: the tubule of the testis is a case in point. It may well be that the really sensitive process is not the turnover of cells *per se*, but the turnover of chemical material within the nucleus. Thus, desoxyribosenucleoprotein has not only been elaborated at some point in time in interphase before cell division, but certainly in the case of the radiosensitive small lymphocyte is being replaced even though the cell is not expected, according to conventional theory, to divide again.

The effects of irradiation on the process of mitosis are readily observed after doses which are known to produce significant effects on the tissue. Following a single dose of x- or γ-rays of about 50r the mitotic rate will be slowed for a while. Following this there may be a rebound phenomenon, the rate increasing to a figure above the average normal. There may thus be phases of depression and apparent stimulation following a short-lived irradiation. With continuous irradiation, such as will occur with internal irradiation from most internally deposited radioactive materials, there will be a depression of mitotic rate, but if the dose is not too great adaptation may occur with a return towards normal in spite of the continuing irradiation. In therapy with radiation or with radioactive isotopes the aim, certainly in cases of cancer, is a concentration of radiation which will not only depress the rate of mitosis but which will cause mechanical damage of the cell-productive works.

The proper progression of events in mitosis is dependent upon the orderly arrangement on the spindle of the divided chromosomes which are to be drawn to the respective daughter cells. The ionizing particles passing through the resting nucleus result, either by direct ionization or

indirectly by physicochemical action, in fractures of the chromosomal material. Any such fracture which does not spontaneously heal results in disordered action at the next mitosis. Daughter cells formed are unbalanced, compared with the normal, in their complement of chromosomes. Subsequent mitotic divisions are then impossible. This is certainly true with normal tissues. Unhappily, malignant growths are not only characterized by a high rate of turnover of cells, which should make them radiosensitive, but often have an abnormal complement of chromosomes: as if, in virtue of their state of malignancy, they had become adapted to a state of imbalance so that a further disorganization by radiation has a smaller than expected effect.

RELATIONSHIP BETWEEN DOSE AND EFFECT

Between most doses of radiation—over and above the normal background—and biological effect there is a relation comparable with the usual response to a noxious substance such as a chemical or bacterial agent. The graph of effect upon dose is sigmoid in shape. Normally one finds so great a variation amongst individuals that it is usual to graph effect versus the logarithm of the dose in order the better to demonstrate the sigmoid form. With radiation, however, there is much more uniformity of response and the relationship is seen when effect is plotted against dose directly. For practically all the biological effects of radiation this expression holds good. There is, however, a classical exception. Ionizing radiation not only produces somatic effects but genetic effects. The rate of gene mutation is increased on exposure of the germ cell to such radiations. The plot of the increase in mutation rate upon dose is a linear function. In the jargon of radiobiological theory it is a 'single hit' effect. One hit on the gene with an ionization leads to the change, whereas to produce the sigmoid shape of graph multiple, more or less simultaneous, events are required.

INDUCTION OF CANCER

It is possible that the induction of malignant change is a similar phenomenon in a somatic cell to genetic mutation in a germ cell. In fact one of the theories of carcinogenesis which waxes and wanes in popularity involves the 'somatic mutation'. Possibly the most suggestive evidence in its support is the observation of the Medical Research Council's committee in 'The Hazards to Man of Nuclear and Allied Radiation' of a more or less linear relationship of the incidence of leukæmia following radiation with dose. Here the time factor over which the irradiation was given seemed of little importance. In most experimental approaches with experimental animals, however, the dose rate as well as the total dose has been a factor of importance in the production or failed production of cancer. Prolongation of the dose in time has usually facilitated induction of new growth. In terms of radioactive materials deposited internally this means that one should beware of those with long effective half-lives in the body and those which have a high focal or tissue concentration.

SOME USES OF ISOTOPES IN RESEARCH

WITH SPECIAL REFERENCE TO TURNOVER STUDIES

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THE basic principle on which the use of isotopes rests in all biological research is the simple fact that the living cell cannot distinguish between the various isotopes of the same element. This statement has a wider meaning in that the cells cannot differentiate even between substances containing the naturally occurring elements and substances containing, in one or more chemical groupings, artificially produced radioactive isotopes of these elements. The same applies to a compound in which the proportion of one of the naturally occurring, but rare, isotopes has artificially been raised. For example it is possible to prepare the amino-acid glycine, $CH_2.NH_2.COOH$, so that 10 to 50 per cent. (or even more) of all its nitrogen consists of the rare, naturally occurring and non-radioactive heavy isotope ^{15}N instead of the normal 0.38 per cent. Preparations of glycine can also be made in which either of its carbon atoms contains a high proportion of radiocarbon ($^{14}CH_2NH_2.CO_2H$ or $CH_2NH_2.^{14}CO_2H$). So far as is known, these variously labelled forms of this amino-acid are treated by animals as their natural counterpart.

'TRACER EXPERIMENTS' IN NATURE

In all natural waters there are two isotopic forms of hydrogen: one has an atomic weight, in round figures, of one (hydrogen=protium, ^1_1H) and the other of two (deuterium, ^2_1H or D). Of all the hydrogen in these waters 99.98 per cent. is protium and only 0.02 per cent. is accounted for as deuterium. When the hydrogen contained in organic substances of living matter is analysed, it is found again that 99.98 per cent. consists of ^1_1H and 0.02 per cent. of ^2_1H. The same principle applies generally to other elements of biological importance also: namely, that the various isotopes of these occur in living organisms in the same proportion as found in their inanimate surroundings. Clearly, if cells were to use preferentially either the lighter or the heavier isotope of any one element in building up their constituents the proportions of these isotopes in living matter would differ from those found in the inanimate world surrounding us. It is immaterial in this respect whether an isotope is stable or radioactive.

One of the radioactive isotopes of carbon, ^{14}C, has a half-life of 6000 years and occurs naturally in minute amounts. This radioactive carbon, in the

form of CO_2, has been 'fixed' through thousands of years by plants by photosynthesis into their organic constituents; animals in turn acquired such ^{14}C mostly by eating the plants. Of course, when the plants or animals die any further accumulation of the ^{14}C ceases, but in such dead remains of plants and animals, or articles manufactured from plant and animal products, that 'survived' the ravages of many centuries the ^{14}C is still detectable. Since, however, ^{14}C decays with a half-life of 6000 years, the amount of this isotope found now in these dead remains depends upon the age of the articles. So constant has been the amount of $^{14}CO_2$ in the atmosphere and its inclusion into living matter that, by careful determination of the proportion of radiocarbon in the carbon of ancient articles, it is possible to calculate their age as far back as 30,000 to 40,000 years with an accuracy of about $\pm$200 years. This method is known as 'carbon dating'.

The two examples quoted are in effect 'tracer experiments' provided by nature. For purposes of laboratory experimentation we have now a wide variety of isotopes to choose from, each suited for a particular purpose. Returning, briefly, to the example of incorporation of naturally occurring $^{14}CO_2$ by plants into their constituents in the course of photosynthesis, an experiment may easily be devised by putting a plant into an atmosphere in which the concentration of $^{14}CO_2$ has artificially been raised and then exposing the plant to light for varying intervals ranging from a few seconds to minutes or hours. By an analysis of the cell constituents for their content of radiocarbon at these intervals a 'pathway' of the CO_2 in the photosynthesis of carbohydrate, for example, may be described. This has in fact been achieved and the various metabolic events in this fundamental process of life are now known in great detail through the use of ^{14}C.

In this number of *The Practitioner* various diagnostic and therapeutic uses of radioactive isotopes are also described. Most of these applications depend upon the incorporation of a suitable isotope, administered to a patient in a relatively simple chemical form, into some more complex tissue constituent, such as the formation of radioactive thyroxine from $K^{131}I$ or the formation of many radioactive organo-phosphorus compounds from inorganic $^{32}PO_4$. All these incorporations depend upon the metabolic activities of the cells and it is in the study of these metabolic processes that isotopes have proved of greatest value.

REGENERATION OF BODY CONSTITUENTS

The first most important discovery made with the aid of isotopic tracers was the realization that the constituents of most tissue cells are in a continuous state of flux, undergoing degradation and resynthesis (Schoenheimer 1941). In an adult animal, whose body weight is kept constant, these two processes, degradation and resynthesis, exactly balance and are responsible for the constant composition of the tissues. Behind this seeming constancy there lies a process of continuous regeneration, which is referred to generally as the turnover of the various body substances. In this connexion two

terms must be defined: (a) turnover time and (b) turnover rate. The *turnover time* of a tissue substance may be defined as the time required for the regeneration of an amount of the substance equal to that contained in the tissue or body fluid. This may vary from some minutes, as in the instance of some organic phosphorus compounds (adenosinediphosphate, adenosinetriphosphate), to several days as in the instance of plasma proteins. The *turnover rate*, of course, can be calculated from (a) and is defined as the amount of a substance that is renewed in a unit length of time. For example, the turnover rate of liver cholesterol in the rabbit is about 50 mg./day/100 g. liver (Popják and Beeckmans, 1950b). Since the rabbit's liver contains 200 to 300 mg. of cholesterol per 100 g., the turnover time of this substance in that organ is 4 to 6 days.

Measurement of either of these two parameters of body substances is of interest not only from a purely academic point of view, but may also be of practical value. Some of the clinical diagnostic uses of radioisotopes depend upon the changes of turnover rates of some body substances: e.g. the diagnosis of thyroid disorders with radioiodine hinges on the altered turnover of various iodine compounds in such diseases. Since the determination of turnover times and turnover rates of various substances often involves the use of isotopically labelled 'precursors', it will be necessary to discuss first what is meant by a precursor. A definition may be arrived at in the easiest way by considering briefly how the regeneration of the various substances in the body is achieved.

Much of our knowledge on this question was gained through the use of isotopes in various researches. It is now known that most biological systems, ranging from a single-cell organism to the vertebrates, manufacture their cell constituents from small molecules in preference to accepting large unchanged molecules from their food. In vertebrates this is achieved by the reassembly of the fragments into which the constituents of diet are usually broken down in the course of digestion, or in the course of metabolic processes occurring outside the digestive tract. The fragments into which the substances contained in the diet or within cells are broken down often provide not only combustible fuel for energy-yielding processes but also the primary building units from which larger molecules are synthesized. For example, fatty acids are broken down to acetic acid and they are also synthesized from acetic acid; furthermore, acetic acid is oxidized in the citric acid cycle and is a most important source of energy in the animal organism. Such a complete interchange of intermediates in the breakdown and synthesis of a substance, however, is not a general rule. Cholesterol is synthesized also from acetic acid but is not broken down to acetate but to bile acids. The protoporphyrin of hæmoglobin is synthesized from a pyrrole, porphobilinogen (Falk, Dresel and Rimington, 1953); the latter is derived from two molecules of δ-aminolaevulinic acid (Shemin and Russell, 1953; Neuberger and Scott, 1953) which in turn is made from the condensation of succinic acid with glycine. In these examples acetic acid may be called the

precursor of both fatty acids and of cholesterol, and cholesterol the precursor of bile acids. Generally speaking the term precursor applies to any substance which can be shown to contribute either specific chemical groupings or its entire carbon skeleton in the formation of another. When the formation of a substance involves several steps, as in the above example of the biosynthesis of protoporphyrins, the substance immediately preceding the final product is called the 'immediate precursor'. Thus, succinate and glycine may be called precursors of porphyrin, but they are immediate precursors only of δ-aminolaevulinic acid.

METHODS OF MEASURING TURNOVER RATES AND TIMES IN BIOLOGICAL SYSTEMS IN A STEADY STATE

The methods to be described in a simplified manner may be applied to systems in which the rate of synthesis of a substance is equal to its rate of degradation; such a system is said to be in a steady state or dynamic equilibrium.

METHODS DEPENDING ON THE ADMINISTRATION OF A LABELLED PRECURSOR IN A SINGLE DOSE

The most frequently employed method for measuring the turnover of a substance depends upon the use of its labelled precursor. For example, in order to measure the turnover of fatty acids or that of cholesterol in the tissues we might inject into an animal acetate labelled either with tritium ($C^3H_3.CO_2H$) or with a carbon isotope, e.g. ^{14}C ($^{14}CH_3.CO_2H$, or $CH_3.^{14}CO_2H$).

Let us assume a hypothetical system in which substance A occurring in the blood is the immediate precursor of substance B in one of the organs and B the immediate precursor of compound C. If a small amount of substance A, suitably labelled with an isotope, is injected intravenously, it will mix with the same substance present in the blood in an unlabelled form. If frequent samples were taken and substance A isolated, it would be found that its specific activity (or its isotope content/unit weight) would vary with time as shown in fig. 1 (curve A). The rate of fall of the isotope content of the blood will depend upon the rate at which substance A is being transferred from the blood to all the tissues and on the rate at which similar, but unlabelled, molecules pass from the tissues into the blood. In other words, the rate of change in the isotope content of the blood will be a function of the turnover of substance A.

Without going into the mathematical reasoning of the calculations, the turnover time t_t, of substance A in the blood may be calculated by the formula $t_t = t_{\frac{1}{2}} \log_e 2 = t_{\frac{1}{2}}/0.693$; where $t_{\frac{1}{2}}$ is the half-life of the substance and is defined as the time required for its isotope content to fall to one-half of the initial value. If the total amount (W) of substance A in the circulating blood volume is known, the turnover rate is given by W/t_t.

If only the turnover time of substance A is required, it is not necessary to isolate substance A, but merely to measure at intervals the radioactivity

contained in a unit volume of blood provided there is no radioactive substance present other than A. The latter condition, however, usually does not prevail for very long after the injection, because, if substance A is an intermediate in metabolism, it will give rise to other labelled substances and these in turn will (or may) appear in the blood.

The change with time in the specific activity of compound B, whose immediate precursor is A, will be of the type shown in fig. 1 (curve B) and the specific activity:time curve of compound C, which is directly derived from substance B, will be related to curve B as shown by curve C. This type of relationship between the specific activity of the immediate precursor and its product was put forward on the basis of mathematical considerations by Zilversmit, Entenman and Fishler (1943a). The curves in fig. 1 illustrate that the specific activity of the product, before its maximum had been reached, is always lower than that of its precursor; at the maximum it is equal to the specific activity of the precursor, and after the maximum, when it begins to decline exponentially, it is higher than the specific activity of the precursor. Zilversmit *et al.* (1943a) have shown that the turnover time of a substance may be calculated from the relationship between the specific activity: time curves of the precursor and of the product.

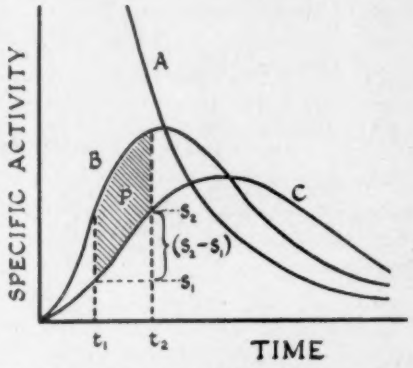

FIG. 1.—Relationship between the specific activities of precursor and product after the administration of a single dose of labelled precursor.

Referring to fig. 1, let the specific activity of compound C at time t_1 be S_1 and at time t_2 be S_2. Then it can be shown that the turnover time, t_t of compound C is given by the shaded area, P, in fig. 1 divided by $(S_2 - S_1)$, i.e. $t_t = P/(S_2 - S_1)$. The area, P, is the area under curve B minus the area under curve C between the two chosen time limits of t_1 and t_2.

It will be readily appreciated that several determinations are required in order to define each curve and that the precursor of the substance investigated must be known. Furthermore, the precursor must occur in the blood or tissues in amounts that will permit its isolation. These conditions severely limit the general usefulness of the method and it is not surprising that in relatively few investigations has it been made use of (e.g. Zilversmit, Entenman and Chaikoff, 1948; Popják and Muir, 1950).

The relationships just discussed can be used also to identify the as yet unknown immediate precursor of a substance. If, using the example given in fig. 1, it is observed that after the administration of labelled substance A only substance B, out of several others tested, is related to compound C

in the manner illustrated by curves B and C, it may be assumed that B is the immediate precursor of C. For example, Popják, Glascock and Folley (1952) found that after the injection of acetic acid labelled with ^{14}C in the carboxyl-carbon ($CH_3.^{14}CO_2H$) to a lactating animal the lactose in the milk and the glycerol of milk fat became labelled, in addition to the fatty acids. The specific activity: time curves of lactose and of glycerol were related to one another as curves B and C in fig. 1. Since there were good reasons for believing that the specific activity of the lactose represented also the specific activity of hexose that was metabolized in the mammary gland, it was concluded that the glycerol of milk-fat was derived in the mammary gland from hexose.

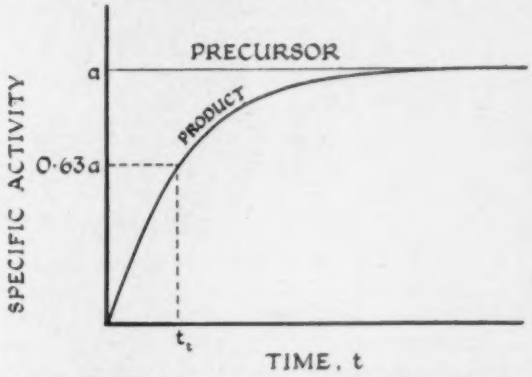

FIG. 2.—Relationship between the specific activity of a substance derived from a labelled precursor when the specific activity of the precursor is maintained constant in the body.

A further comment is required here on the use of single doses of isotopically labelled precursors for the measurement of turnover rates. As we have seen, after the administration of a single dose of a labelled precursor, the specific activity of the substance derived from it will vary continuously with time. It is therefore rarely, if ever, possible to obtain quantitatively useful information regarding turnover rates from measurements made at one time interval after the administration of the labelled substance. Also, if substance A is converted into C through a series of intermediates and the immediate precursor of C is not known, then absolute values of turnover rates for C cannot be established. Nevertheless, the rate of incorporation of the label into C relative to the amounts of isotope present in A can give very useful data in certain types of investigation, as for example in deciding whether an experimental treatment alters the rate of metabolism of C or not.

METHODS DEPENDING ON THE CONTINUOUS ADMINISTRATION OF A LABELLED PRECURSOR

In another technical approach to the measurement of turnover times the labelled precursor is administered at frequent intervals in small doses, or continuously, for several hours or days, the aim being to maintain the specific activity of the precursor in the body at a constant level. In this instance the specific activity of a substance derived from the precursor will gradually rise in a manner shown in fig. 2.

Let the specific activity of the precursor in the body be a, constant, and that of its product at any time, t, be y. If the turnover time of the product is t_t, then it can be derived mathematically (Zilversmit *et al.*, 1943a) that its specific activity, y, will vary with time according to equation (1): $y = a(1 - e^{-t/t_t})$ (1) where e is the base of the natural logarithm. At turnover time $t = t_t$ and $y = a(1 - e^{-1}) = 0.63a$. In other words, at turnover time the ratio of the specific activity of the product to that of the precursor (y/a) will be 0.63. Equation (1) may be put into another form; at any $1/n$-th fraction of the turnover time $t = t_t/n$ and we can write $y/a = (1 - e^{-1/n})$ (2). Since the ratio y/a can be determined at any time t, the value of n can be calculated from equation (2) and hence the turnover time is obtained by $t_t = nt$.

This type of experimental technique has much in its favour particularly when the precursor can be administered conveniently either in food or drinking water. The number of determinations required to obtain data for the calculations is much fewer than after the administration of a single dose of the labelled precursor. Theoretically one single determination should suffice provided one can be reasonably well satisfied that the specific activity of the precursor has in fact been maintained constant.

USE OF LABELLED WATER FOR MEASURING TURNOVER TIMES

A special case of this experimental approach is the use of either heavy water, D_2O (deuterium oxide), or of radioactive water, T_2O (tritium oxide), in the measurement of rates of synthesis of body constituents. In many biological syntheses the intermediates resulting from the condensation of small molecules are reduced with hydrogen. The best examples of this type of reductive syntheses are the formation of fatty acids and of cholesterol from acetic acid. The hydrogen donors for these reductive reactions are in rapid equilibrium with the hydrogen of body water. If therefore such syntheses occur in an environment containing labelled water (D_2O or T_2O) the hydrogen isotope will be incorporated into the newly formed molecules at every point where reduction occurs. It is particularly easy to maintain constant the concentration of either D_2O or T_2O in the body of a subject by first injecting an amount of saline, made up with a chosen concentration of the labelled water, in order to bring the concentration of, say, D_2O in the total body water to 1 per cent. and then to replace the drinking water with 1.5 per cent. D_2O. The concentration of D_2O in the body can be kept steady at about 1 per cent. level for days or weeks.

In the first extensive use of an isotope for metabolic investigations Schoenheimer and his colleagues (Schoenheimer, 1941) employed this very technique. The formulæ, (1) and (2), given in the previous section, however, cannot be applied without modification because the final concentration of the hydrogen isotope in the newly synthesized molecules will not be the same as in the body water but somewhat lower, depending upon the number of positions reduced in the molecule. For example, in the case of saturated fatty acids, when all the fat has been newly synthesized, the concentration of the hydrogen isotope will be only 50 per cent. of that found in body water (Schoenheimer, 1941); for cholesterol this value is 63 per cent. (Popják and Beeckmans, 1950b). In other words, the concentration of the

hydrogen isotope in each substance will tend to a maximum characteristic of that substance.

If the maximum isotope concentration attainable in a substance under these conditions and after prolonged maintenance on labelled water is i_m, then the isotope concentration, i, in the substance at any time, t, will be related to the turnover time, t_t, according to equation (3): $i = i_m(1 - e^{-t/t_t})$ (3) from which the turnover time may be calculated as from equation (2). The only condition of this method is that i_m must be determined for each substance in experiments of long duration. Fortunately this value is now available for substances for the study of which labelled water can be used (lipids and carbohydrates).

This method is also of interest because, with minor modifications, it can be used for the evaluation of both rates of synthesis and rates of degradation of substances in a biological system which is not in a steady state, for example in the growing embryo. Under conditions of growth synthesis must outstrip the degradative processes and therefore the concept of turnover cannot be applied; instead one must define both the rates of synthesis and rates of degradation. It was by the application of this method that Goldwater and Stetten (1947) measured the rate of synthesis and degradation of fœtal glycogen and Popják and Beeckmans (1950a) evaluated the same parameters for fœtal lipids. To illustrate the deviation from a steady state it may be of interest to mention that in the rat fœtus on the 19th day of pregnancy 5 mg. of glycogen are synthesized per 1 g. body weight per day; of this, 3 mg. are degraded and 2 mg. deposited. In the liver of the rabbit fœtus on the 28th day of gestation 1.64 mg. of cholesterol are synthesized and 0.82 mg. degraded, resulting in a net accumulation of 0.82 mg. Similar conditions must prevail also in tumours.

DETERMINATION OF TURNOVER RATE OF A SUBSTANCE IN BLOOD

The turnover rate of almost any of the constituents of the blood plasma can be determined if, instead of labelled precursor, the compound in question is introduced into the circulation in a labelled form. Since, according to the concept of the dynamic equilibrium of body constituents, the rate of appearance and rate of disappearance of a substance are equal in the 'steady state', the turnover rate can be measured from the rate of disappearance. In the first method described in this article and illustrated in fig. 1 the turnover time of precursor A in the blood was calculated on the basis of this principle from the half-life of compound A in the blood. The half-life of a metabolite, such as acetate, glucose or an amino-acid in the blood, is usually very short, and is measured in minutes. The half-life of larger molecules, such as lipids and proteins, is, however, much longer: several hours or days. It is often not feasible to extend the period of observation beyond a few hours and therefore turnover rates must be calculated from data obtained before the half-life period had been reached.

If, after the intravenous injection of a labelled substance, e.g. phospholipid or protein, the specific activity of the total substance in the blood is S_0 and after a

time, t, the specific activity is S_t, then it can be shown that $S_t = S_0 e^{-t/t_t}$ (4), where e is the base of natural logarithm and t_t the turnover time of the substance. By taking the natural logarithm on both sides of the equation we have $\log_e S_t = \log_e S_0 - \frac{1}{t_t} t$ (5). It follows from equation (5) that if the logarithm of the specific activity of the substance in the blood is plotted against time, a straight line is obtained provided our assumptions regarding the 'steady state' are correct. The slope of the straight line will be $\left(-\frac{1}{t_t}\right)$: i.e. the reciprocal of the turnover time (with a minus sign). Of course, if the amount of the substance in the circulating blood is known, the turnover rate can also be calculated.

This approach to turnover studies on blood constituents was made for the first time by Hahn and Hevesy (1939) in their investigations on plasma phospholipids. Zilversmit, Entenman, Fishler and Chaikoff (1943b), however, presented more extensive data on the same subject and have shown that the experimental observations permit the theoretical treatment just outlined.

The turnover of plasma proteins can be measured according to the same principles. All that is needed for this purpose is the preparation of a suitably labelled plasma protein. This can now be done quite satisfactorily *in vitro* with radioactive iodine. It has been shown that mildly iodinated plasma proteins behave as their normal fellows (McFarlane, 1956) and therefore such preparations can be used for turnover measurements.

CONCLUSION

The outline given in this article of the concept of dynamic equilibrium and of turnover measurements is of necessity sketchy, but the aim has been to stress principles rather than details. The use of isotopes in biological research is now so extensive that within the scope of a short article only some of those aspects of the subject could be treated that might be of use in the study of normal and disordered human metabolism.

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RADIOACTIVE ISOTOPES IN DIAGNOSIS

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THE use of radioactive isotopes in clinical investigation is still a relatively new procedure as there has been a freely available supply from nuclear reactors for less than ten years. During this period they have been used in many ways in the study of human disease. Some isotopes are now regularly employed in certain centres as diagnostic aids, whilst others are reserved for the investigation of special problems and unusual cases. However, with such new tools no clear-cut division between clinical research and diagnostic use is possible.

Certain general principles underlie the use of radioactive isotopes in the investigation of disease processes. The tissues of the body handle in the same way both the natural form and the radioactive isotope of an element. The latter, however, can be readily followed and measured by the characteristic radiations which it emits. The type of measuring device chosen depends upon the nature and energy of this radiation, but the radioactivity in any fluid sample can usually be measured easily and accurately. Furthermore, the concentration of a radioactive isotope can often be ascertained in a particular structure or region of the body if the radiation is sufficiently penetrating to reach an overlying counter.

A radioactive isotope may be administered in a simple inorganic form to trace an element naturally present, such as sodium or iodine. It may be built outside the body into a complex molecule and then administered in this form in order to follow the metabolism of the whole compound. For example, much can be learnt about the absorption of vitamin B_{12} if a radioactive isotope of cobalt is used in its preparation. Some cells of the body take up and bind certain elements relatively firmly. In this way red blood cells can be labelled and their survival after transfusion can be followed. Many radioactive isotopes have been employed in clinical investigations and in a short survey these cannot all be recorded and discussed. Only a few of the more commonly used procedures will be considered as examples of the use to which these new tools may be put.

THYROID DISORDERS

The normal thyroid gland concentrates iodide from the plasma and utilizes it in the synthesis of thyroxine, which in due course is passed into the blood stream where it is bound to the plasma proteins. The true measure of thyroid activity is the rate at which its hormone is released into the circulation, but this is difficult to determine directly. The movement of

iodide into the thyroid gland and its subsequent transfer into the blood in protein-bound form can be traced by the use of radioactive isotopes of iodine (Hamilton and Soley, 1939; Werner *et al.*, 1949; Goodwin *et al.*, 1951). The ones in common use are ^{131}I and ^{132}I. Both emit β- and γ-radiations and the latter can readily be detected by an external counter placed over the thyroid. In this way the fraction of the dose of the isotope present in the gland can be measured. The amount excreted in the urine can be determined provided that a complete collection is made. Radioactive iodine may be present in the blood either in the inorganic form before it has been taken up by the thyroid, or in an organic form after passage through the gland. The half-life of ^{131}I is eight days and it is more convenient to use and is easier to prepare. Measurements of its concentration in the thyroid and blood stream can be made for several days after its administration. It does, however, give a greater radiation dose to the gland than ^{132}I, which has a half-life of 2.4 hours, and when repeated tests are required or investigations are being made in young patients ^{132}I is the isotope of choice.

The use of radioactive iodine in the diagnosis of hyper- and hypothyroidism depends upon the assumption that the distribution of the tracer dose between the thyroid, blood, and urine reflects the activity of the gland in the synthesis and secretion of hormone. The interpretation of the tests is usually straightforward but may be difficult or impossible if the function of the gland has been altered either by previous iodine excess or deprivation or by antithyroid drugs, radiotherapy or surgery.

Tests of thyroid function with radioactive iodine rely on the measurement of either the rate of radioiodine transfer into the gland or of the amount that has arrived in the plasma after passage through the gland. Tests of the first type include simple measurements of uptake of radioiodine at intervals after administration of the dose, determination of the clearance of radioactive iodine in inorganic form from the blood by the thyroid, and measurements of the amount of radioactive iodine excreted in the urine, which forms an indirect assessment of the quantity that has been retained in the thyroid gland. The second type of test depends upon the determination of the amount of protein-bound radioactive iodine forty-eight or seventy-two hours after administration of the dose. A more reliable diagnosis can be made if two or more tests are used in combination, preferably one of the first type in association with a measurement of protein-bound radioactive iodine. The sensitivity of the different tests varies according to the nature of the thyroid disturbance and they have been extensively reviewed in recent years (Pochin, 1950; Myant, 1952; Foote *et al.*, 1952; Wayne, 1954; Fraser, 1956).

It is difficult to lay down standards for the diagnosis of thyrotoxicosis and myxœdema on radioactive iodine tests. A wide variety of investigations is in use and each laboratory has to decide its range of normal values. These may vary from centre to centre, depending upon the type of equipment in use, the degree of accuracy attained and possibly on local conditions re-

garding the supply of iodide in food and water. In the diagnosis of thyrotoxicosis in Sheffield reliance is placed on the measurement of the radioactive iodine content of the thyroid gland and the protein-bound ^{131}I content of the serum.

In the majority of untreated thyrotoxic patients the uptake at four hours exceeds 40 per cent. of the dose and the protein-bound ^{131}I concentration in the serum at forty-eight hours is greater than 0.4 per cent. per litre (Wayne, 1954). The thyroid clearance rate in normal subjects at two hours after oral administration is usually between 10 and 60 ml./min. In thyrotoxic patients the rate is usually above 80 ml./min. and as a rule greatly exceeds this value.

The simplest test is the measurement of the neck-thigh ratio.

The more radioactive iodine that is taken up by the thyroid the less there is available for distribution elsewhere in the body. At two hours after an oral dose given to a fasting patient the radioactivity due to radioiodine is measured over the neck and thigh and the result is expressed as a ratio. Under the conditions described by Pochin (1950) the ratio seldom exceeded 7 in normal subjects and higher values were characteristically found in hyperthyroidism.

In diagnosing hyperthyroidism with radioactive iodine tests there are certain possible sources of error apart from technical inaccuracy. A high uptake of radioactive iodine occurs apart from thyrotoxicosis in a thyroid previously starved of iodine, as may be seen in endemic goitre or immediately after a period of treatment with antithyroid drugs. High levels of protein-bound radioactive iodine are still found after the successful treatment of thyrotoxicosis by surgery or radiation.

In hypothyroidism, the diagnosis is not so easily confirmed by tests with radioactive iodine. The uptake by the thyroid is depressed but in many mild cases there is a considerable overlap with the normal range. In this condition the urinary excretion of radioactive iodine is increased and the diagnosis may be confirmed by collecting the urine over different periods as described by Fraser *et al.* (1953). Although this is probably the most satisfactory radioactive iodine method for establishing the presence of hypothyroidism, it depends for its reliability upon accurate timing and completeness of urine collections and is inconvenient for the outpatient, who has to take away three large bottles.

In attempting to assess thyroid function with radioactive iodine it is unwise to attempt to draw a strict dividing line between the normal and abnormal, as there are all gradations of underactivity and overactivity. Nevertheless, in cases in which the diagnosis is in doubt on clinical grounds, great assistance can usually be obtained from radioactive iodine tracer studies. However, the decision as to whether therapy is required must be based on all the available criteria, both clinical and laboratory, and should never be made solely on the basis of radioactive iodine tests.

The radiation hazard to the thyroid gland must always be considered when these tests are contemplated. Obviously, if the diagnostic tests are preliminary to therapy with ^{131}I the tracer dose employed is negligible. If the test is to include a measurement of protein-bound radioactive iodine ^{131}I must be used and a dose of about 25μc. is usually required. This isotope

in such a dose should not be used in infants or children as in them the danger of producing malignant change in the thyroid with ionizing radiations is apparently greater than in adults (Simpson, Hempelmann and Fuller, 1955; Clark, 1955; Kilpatrick *et al.*, 1957). It should also be avoided in pregnancy and in lactating mothers as the ^{131}I is concentrated in the milk (Miller and Weetch, 1955). If radioactive iodine diagnostic tests are essential in cases of this type, ^{132}I should be used, but, with its short half-life, only an uptake and clearance rate can be satisfactorily measured.

The diagnostic use of radioactive iodine in carcinoma of the thyroid is considerably limited. Undifferentiated and most papillary tumours do not take up iodine and even in the more differentiated follicular carcinomas it is unusual to find much concentration of iodine. It is difficult to demonstrate radioactive iodine in a tumour if normal thyroid tissue is also present as the latter always possesses much greater ability to concentrate iodine. If, however, all the normal thyroid tissue has been removed by surgery or destroyed by radiation, a proportion of a tracer dose of radioactive iodine may occasionally be taken up by the primary tumour and the metastases. This may be demonstrated either in an autoradiograph made from a biopsy specimen or by external counting over an area where a metastasis is suspected. This affords confirmation of the nature of the tumour and evidence that it is suitable for treatment with radioactive iodine.

HÆMATOLOGICAL DISORDERS

Cobalt-labelled vitamin B_{12}.—Cobalt is an essential constituent of vitamin B_{12} and in the biosynthesis this element can be supplied in a radioactive form as ^{56}Co or ^{58}Co which have half-lives of 80 and 70 days respectively (Booth and Mollin, 1956; Baker and Mollin, 1955; Bradley *et al.*, 1954). These isotopes are now used for clinical investigations in preference to ^{60}Co which has a half-life of 5.3 years, but was used in the earlier studies (Heinle *et al.*, 1952). In pernicious anæmia the absorption of vitamin B_{12} is grossly impaired owing to the absence of the intrinsic factor secreted by the normal stomach. After a dose of vitamin B_{12} labelled with radioactive cobalt is given by mouth to a patient with pernicious anæmia, 75 per cent. or more is recovered in the fæces, whereas in a healthy individual less than 40 per cent. is excreted in this way (Callender *et al.*, 1954). If at the same time as the oral administration of the labelled vitamin B_{12} a parenteral injection of a large dose of 1 mg. of ordinary unlabelled vitamin B_{12} is given, the radioactive material absorbed is in large measure flushed out in the urine (Schilling, 1953). In such circumstances in healthy individuals much of the radioactive dose absorbed from the intestine is recovered in the urine, whereas in patients with pernicious anæmia the urinary excretion is negligible. As it is much easier and pleasanter to work with urine rather than fæces the second type of test is more popular. It is, however, unnecessary and undesirable to use this test in the investigation of straightforward cases of pernicious anæmia which can be more satisfactorily diag-

nosed by the examination of the peripheral blood, bone marrow and gastric juice. Tests of this type should be strictly reserved for the investigation and precise diagnosis of obscure types of megaloblastic anæmia.

Labelling of red blood cells with ^{32}P, ^{51}Cr and ^{86}Rb.—These isotopes of phosphorus, chromium and rubidium are taken up by red cells and retained in them with varying degrees of firmness (Reeve and Veall, 1949; Gray and Sterling, 1950; Mollison and Veall, 1955; Tudhope and Wilson, 1956). The red cells labelled in this way can be reinjected into the circulation. The extent of the dilution of the radioactive cells affords a measurement of the total red cell volume:—

$$\text{Red cell volume} = \frac{\text{Radioactivity injected in labelled cells}}{\text{Radioactivity per unit volume of red cells in the circulation}}$$

Sufficient ^{51}Cr is taken up within half an hour by a suspension of red cells at room temperature and a measurement of red cell volume can be completed within two hours of withdrawing the initial blood for labelling.

Investigation of red cell volume is still essentially a research procedure but it is clear that the use of ^{51}Cr affords a rapid method of measurement which may prove to be of considerable practical use in the assessment of the extent of hæmorrhage. A further advantage is that the ^{51}Cr is securely retained in the labelled cells and after their destruction is not taken up by new cells. The survival of the cells can thus be followed in the blood for several weeks (Ebaugh *et al.*, 1953; Read *et al.*, 1954). One practical use of this observation is in testing the compatibility of blood for transfusions in difficult cases (Mollison and Cutbush, 1955). A very small fraction of the cells to be transfused is labelled with ^{51}Cr and injected into the recipient. Their survival can be followed by serial measurements of the radioactivity of the blood. If the cells are incompatible the radioactivity drops sharply as they are rapidly removed from the circulation.

Absorption and utilization of ^{59}Fe.—A radioactive isotope can be used to measure the extent of absorption of iron given by mouth. The utilization of radioactive iron after either absorption from the alimentary canal or parenteral injection can be studied by measuring the amount of radioactivity that appears in newly formed red cells. Many interesting investigations into the mechanism of the development of anæmia have been made in this way but these techniques still remain essentially in the field of research rather than of clinical diagnosis.

THE CIRCULATION

Radioactive isotopes have been used in many ways to study the circulation. The velocity of blood flow has been measured in the veins of the lower limb by injecting radioactive sodium into a vein on the dorsum of the foot and timing its arrival under a counter placed over the groin. Slowing of the rate of venous blood flow may be an important factor in the development of venous thromboses (Wright, 1952). Attempts have also been made to measure the efficiency of local circulation by injecting a small quantity

of ^{24}Na in isotonic solution into a deep structure such as muscle. The removal of the ^{24}Na can be determined by placing a suitable external counter over the depot. One factor in determining the rate of disappearance of the radioactive sodium from the injection site is the blood flow in the surrounding capillaries (Kety, 1949), although there are probably other factors of importance not directly related to the circulation (Miller and Wilson, 1951; McGirr, 1952). Practical use has been made of this technique in determining the viability of skin flaps in grafting operations. If the proximal end of the graft is clamped a normal rate of removal of injected radioactive sodium indicates that a satisfactory circulation has been established through the distal end (Barron and Veall, 1952).

WATER AND ELECTROLYTE METABOLISM

In the investigation of water and electrolyte abnormalities, the only methods of study until recently were the measurement of the concentration of electrolytes in body fluids, particularly the plasma, and the performance of a metabolic balance study. The latter, which may involve the measurement of the intake and output of potassium, sodium and chloride, is capable of demonstrating a gain or loss in the body content of these elements over the period of study. By these methods alone, however, the total amount in the body cannot be determined. This can now be done by the use of radioactive isotopes. For example, if ^{24}Na, a radioactive isotope of sodium, is injected intravenously it rapidly mixes with the stable ^{23}Na in the body. The extent of the dilution of the radioactive sodium in the body pool is measured and the total mass of sodium in the body available for exchange with the isotope can be calculated (Miller and Wilson, 1953). Using techniques of this type, the total 'exchangeable' amounts of potassium, chloride and water present in the living patient can be determined. These investigations are still confined for the most part to the elucidation of research problems but they are adding considerably to our knowledge of the distribution of water and electrolytes in both health and disease (Moore *et al.*, 1954).

LOCALIZATION OF CEREBRAL TUMOURS

It is often difficult to be certain of the presence and position of a cerebral tumour, even after the most detailed clinical and radiological examination. One advance in this problem has been made by using radioactive isotopes. A substance which is concentrated in actively growing tissue is injected in a labelled form so that its distribution within the brain can readily be followed. Cerebral tumour tissue takes up more than the surrounding normal brain. As might be anticipated in these circumstances, vascular tumours such as meningiomas, glioblastomas and metastatic carcinomas are more readily diagnosed than the better differentiated and more slowly growing astrocytomas.

Two techniques have been used. The first depends upon the internal exploration of the skull with a small counting device (Selverstone *et al.*,

1949; Morley and Jefferson, 1952). Radioactive phosphate in the form of ^{32}P is given before operation and then a miniature Geiger counter designed in the form of a probe is passed through a burr hole into the brain. Phosphate is concentrated in rapidly growing tumours and a region of increased radioactivity may represent the site of a neoplasm. In this way the neurosurgeon is guided to the lesion and a biopsy can be taken from the appropriate region with minimal disturbance of normal tissue.

The second method uses the same principle of concentration in rapidly dividing cells but uses an external counting system. Localization depends upon counting at many points over the skull. In these conditions a radioactive isotope must be used which emits gamma radiation, and ^{32}P, a pure β-emitter, is not suitable. ^{131}I has been most extensively employed either in the form of diiodofluorescein or iodinated human serum albumin (Peyton *et al.*, 1952; Dunbar and Ray, 1954; Seaman *et al.*, 1954). These external counting techniques may be helpful when the neoplasm lies in a cerebral hemisphere. When it is situated in the posterior fossa, at the base of the brain, or in the pituitary region, the method is at present of doubtful value.

RADIATION EXPOSURE AND HEALTH HAZARDS IN DIAGNOSTIC TESTS

Increasing attention is now being paid to the possible dangers to health of ionizing radiations, and there is evidence that they may be a factor in leading to the development of malignant disease (Medical Research Council, 1956). In man the investigations have chiefly concerned the long-term results of external x-irradiation in relation to the subsequent development of leukæmia and carcinoma of the thyroid. It is possible that infants may be more susceptible in this way than adults. There is every reason to suppose that internal irradiation of tissues from administered artificial radioactive isotopes carries the same dangers as an equivalent exposure to ionizing irradiation from an external source. Information about the precise hazards is still meagre and it is important to preserve a sense of proportion. The incidence of malignant change after exposure to irradiation is extremely low and the diagnostic aid that can be obtained from properly applied tracer tests with some radioactive isotopes may be great. Like many powerful modern pharmacological agents, ionizing radiations can be both beneficial and harmful and knowledge and judgment are required in their application.

The danger of malignant disease following irradiation apparently increases in proportion to the dose. In all diagnostic tests involving radioactive materials, the exposure should be kept as small as possible. Advances in the design of counting equipment permit accurate measurements to be made with smaller doses of radioactive isotopes. Short half-life isotopes should be used whenever possible, for example ^{24}Na (half-life 15 hours) in preference to ^{22}Na (half-life 2.3 years). Particular care must be exercised if the isotope is liable to be concentrated in a certain tissue and retained in the body. For instance, much sodium is incorporated and firmly fixed in growing bone,

and for this reason the long half-life sodium isotope should not be used in children. In other cases it may be possible to flush out from the body much of the radioactive material at the end of the test by giving a large dose of the corresponding non-radioactive material, as in the vitamin B_{12} tests with labelled cobalt. In these and many other ways the radiation dose can be substantially reduced and this should always be the constant aim of the doctor and physicist in the use of all diagnostic procedures involving exposure to ionizing radiations.

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RADIOACTIVE ISOTOPES IN THERAPY

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In 1948, artificially produced radioactive isotopes first became available for use in medicine in Great Britain. The early optimistic and ill-founded hopes of obtaining a high rate of dramatic cures in malignant disease by means of these isotopes has not been realized. Nevertheless, some of the artificially produced radioactive isotopes have contributed real and fundamental advances in the treatment of many types of malignant disease, and in certain sites (e.g. polycythæmia vera) these isotopes offer the best form of treatment.

The ideal method of treating malignant disease would obviously be by means of a non-toxic chemotherapeutic agent acting specifically, in a lethal manner, on neoplastic cells. In spite of great ingenuity, effort and expense, no such 'aqua vitæ' has yet been discovered. Another approach to this vital problem would be the discovery of any substance possessing the characteristic of being specifically and permanently concentrated to a high degree by neoplastic cells. By artificial means such a substance could be produced in radioactive form and the malignant cells specifically concentrating such a radioactive substance would bring about their own destruction. At present the only such substance in clinical use is radioactive iodine (^{131}I and ^{132}I).

In the treatment of malignant disease artificially produced radioactive isotopes are used in many and varied forms. The selection of any particular isotope technique is in large measure dictated by the exact requirements of the case under consideration. The wide variety of techniques available for the treatment of certain malignant processes by means of radioactive isotopes affords a most flexible, adaptable, essential tool to the armamentarium of the radiotherapist. The clinical applications of the therapeutic uses of isotopes are comparatively new, with the result that modifications and improvement in techniques are constantly taking place.

ARTIFICIALLY PRODUCED RADIOACTIVE ISOTOPES USED FOR EXTERNAL IRRADIATION

The great advantages of high energy irradiation in the 1 to 4 million volt range (i.e. supervoltage therapy), over conventional x-ray therapy machines of around 250 kV, have become fully appreciated in recent years. With such high energy beams skin reactions are minimal, systemic upset very much less, penetration is greater and higher tumour doses can be delivered with greater accuracy. Certain artificially produced isotopes (Cobalt-60, Cæsium-137) emit radiations of high energy and are now obtainable in high

activities of around 1000 to 2000 curies. These isotopes are used as sources of high energy radiation and because of their high activity they can be used at treating distances of 50 to 100 cm., thus giving the equivalent of super-voltage x-ray machines (fig. 1). The 'radium bomb' (fig. 2), containing 5 to 10 grammes of radium element, has been in use in a number of radiotherapy units for many years. Such low activity sources require short treating distances (i.e. skin-source distance) of 5 to 8 cm.—because of the inverse square law the intensity of radiation falls off rapidly. This type of apparatus is only suitable for the treatment of superficially placed malignant lesions, e.g. larynx and pharynx. Artificially produced radioactive cobalt (^{60}Co) may be used as the radiation source in place of radium element.

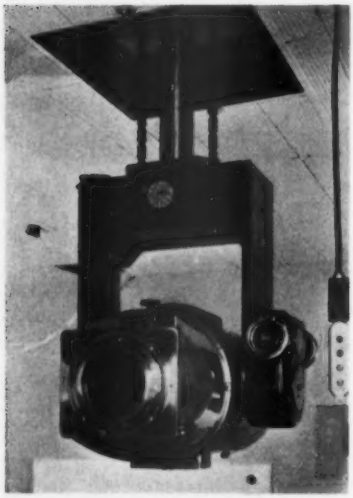

FIG. 1.—The telecæsium (^{137}Cs) unit recently installed in the Downs branch of the Royal Marsden Hospital. This is the first apparatus of its kind in clinical use in this country.

RADIOACTIVE ISOTOPES USED FOR IMPLANTATION (i.e. INTERSTITIAL TECHNIQUES)

In certain sites (e.g. tongue and urinary bladder) circumscribed malignant lesions can often be treated most effectively by local implants of radioactive substances directly into the growth and the immediately adjacent tissues. Such methods permit the irradiation to be confined to a small volume of tissue which can be treated to a relatively high dose level over a period of approximately seven days. If this technique is used it is essential that the radioactive sources should be implanted with absolute accuracy and precision. Until recent years only radium needles or radon seeds were available for this method of treatment and, because of mechanical and technical difficulties, it was often impossible to

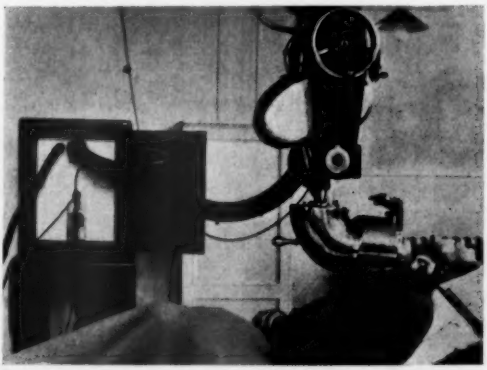

FIG. 2.—The radium-bomb irradiating sub-mental region. Note the safe to which the radium is transferred pneumatically when not in use.

obtain accurate disposition of the radioactive sources. Many of the technical difficulties pertaining to interstitial techniques have been overcome by using artificially produced radioactive isotopes.

Radioactive tantalum wire (^{182}Ta), coated with a thin (0.1 mm.) layer of platinum to absorb the beta-rays, can be implanted with a high degree of accuracy, by means of a special introducer (fig. 3), into the muscle wall of the bladder in certain cases of cancer of the urinary bladder (fig. 4, 5). As these wires are flexible, they accommodate themselves to the varying contours of the bladder wall, and when the period of irradiation has been completed they can easily be removed per urethram. In the treatment of certain bladder neoplasms this technique offers many advantages over the older methods employing radium needles and radon seeds. Because of its flexibility tantalum wire proves a most suitable substance for the preparation of external applicators (moulds) used in the treatment of skin cancers, especially when convex or concave surfaces are involved.

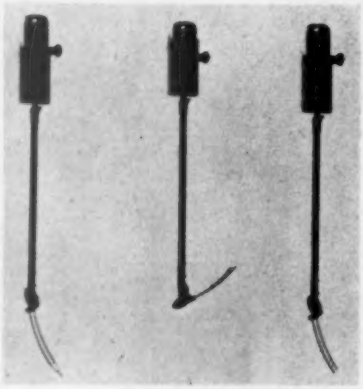

FIG. 3.—Radioactive tantalum wire introducer.

Radioactive cobalt needles are now often used as a substitute for radium needles. Small cobalt beads may be loaded inside thin nylon tubes which are used to implant malignant growths in certain sites; these flexible sources can readily be withdrawn from the tissues without having to perform a second 'operation of exposure'. The implantation of platinum-coated gold grains by means of a special gun (Royal Marsden Hospital pattern, fig. 6) offers a most convenient method of applying interstitial irradiation (fig. 7). Magazines, each containing 15 grains, are irradiated in the atomic pile; they can be obtained at short notice and if not used can be re-irradiated. The gun, when primed, will deliver 15 grains (i.e. the contents of one magazine) at one loading. For routine use these grains offer many advantages over radon seeds.

FIG. 4.—Two radioactive tantalum 'wires' in position in bladder tumour.

In recent years the importance of

'hormone-dependence' in tumour growth (e.g. breast and prostate) has become fully appreciated. On this basis various methods are used to alter the hormone balance of the patient in the hope of inducing tumour regression. Cases of advanced carcinoma of the breast, which have failed to respond to all forms of routine treatment, may at times derive some benefit from pituitary ablation. This measure can be accomplished by implanting a radioactive source into the pituitary gland (fig. 8) by means of a long needle introduced transnasally through the sphenoidal air sinus and the floor of the pituitary fossa. Pellets of radioactive yttrium oxide (^{90}Y) are most suitable for this technique as this isotope emits only beta-rays. These rays are highly destructive, but act over a very short distance, thus producing a small zone of necrosis and thereby a local 'radiation hypophysectomy'. High-activity radon seeds were used in some centres, but the additional gamma-rays from this source possess much greater powers of penetration and some patients so treated developed delayed radiation-induced optic nerve damage. Only a small proportion of patients treated by this technique derive any appreciable benefit.

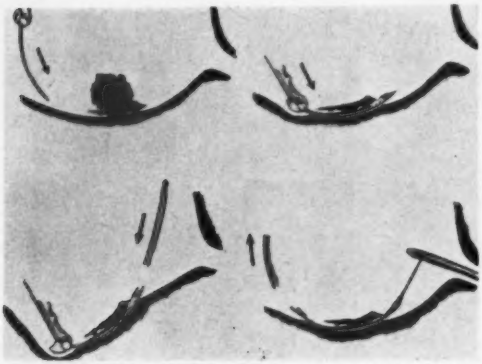

FIG. 5.—Implantation of bladder tumour, using radioactive tantalum wire.

Beta-ray applicators.—Beta-rays penetrate the tissues for only very short distances (1 to 2 millimetres) and this characteristic is utilized in the treatment of certain superficial lesions. Beta-ray therapy is often used in the treatment of pathological processes involving the eye (e.g. Mooren's ulcer, superficial punctate keratitis, rosacea keratitis, vascularization of the cornea and allergic conjunctivitis). This type of radiation is most conveniently given by means of a plastic eye-shell (fig. 9), which is coated with radioactive strontium (^{90}Sr). Radioactive phosphorus (^{32}P) can be incorporated in polythene sheets and used in the treatment of certain skin conditions.

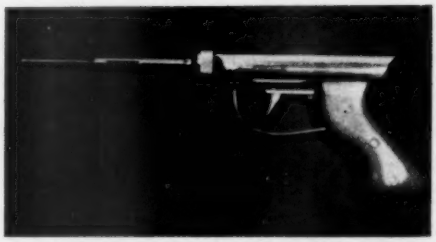

FIG. 6.—Royal Marsden Hospital pattern gun used for the implantation of radioactive gold grains.

RADIOACTIVE ISOTOPES USED LOCALLY IN LIQUID FORM

Malignant disease arising primarily in various sites (especially breast, lung and ovary) often involves the pleural or peritoneal membrane, causing the formation of massive effusions of fluid. These effusions give rise to marked symptoms and require frequent aspirations. If left untreated the patient is soon reduced to a sorry state of misery.

FIG. 7.—Radioactive gold grain implant of secondary malignant gland.

The instillation of radioactive colloidal gold (fig. 10) into the involved serous cavity, following the aspiration of as much fluid as possible, gives rise to appreciable benefit in 30 per cent. to 50 per cent. of patients so treated. A colloid is used in order to prevent the absorption of gold into the blood stream. After the injection of the colloidal gold the patient is tipped into various positions in order to bring all parts of the involved serous cavity into intimate contact with the colloid. Radioactive gold in colloid form emits mainly beta-rays, as well as a small proportion of gamma-radiation. The gold particles are fairly rapidly deposited on the serous membrane where the radiation gives rise to some degree of fibrosis, which is probably mainly responsible for the inhibition of fluid formation. The full benefit from this form of treatment may take some weeks to manifest itself. Following the intracavitary insertion of radioactive colloidal gold, effusions often re-form quite rapidly. If this postoperative fluid gives rise to appreciable symptoms it can safely be aspirated any time after the fifth day—by then nearly all the radioactivity has been taken up by the serous membrane and any fluid that is aspirated possesses little or no activity.

FIG. 8.—X-ray of skull, showing yttrium pellet implant of pituitary gland.

Malignant disease of the urinary bladder may, in a small proportion of cases, first present in the form of multiple small superficial tumours, diffusely spread over all areas of the bladder (fig. 11) with intervening areas

of mossy abnormal pre-malignant mucosa. The proper management of this type of lesion requires treatment to be directed to the whole of the bladder mucosa. This aim can be accomplished by using some form of intravesical irradiation. Such techniques can be administered by introducing radioactive colloidal gold via a catheter or by inserting into the cavity of the bladder a special type of balloon catheter (fig. 12) which is filled with radioactive bromine. By virtue of the proximity of the radiation sources to the bladder wall these techniques give a rapid 'fall-off' in the intensity of irradiation; it is therefore possible to administer a high dose of irradiation to the surface mucosa and at the same time spare the underlying tissues of the bladder wall from excessive damage.

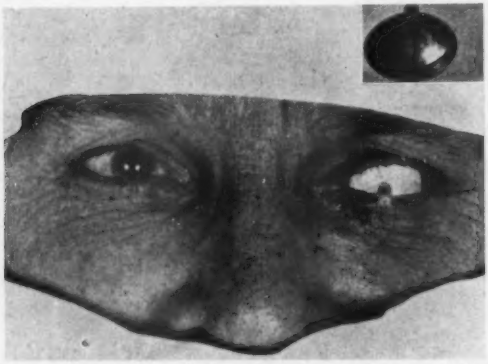

FIG. 9.—Beta-ray applicator: strontium (^{90}Sr) eye-shell.

RADIOACTIVE ISOTOPES IN LIQUID FORM USED SYSTEMICALLY

In this category the isotopes in common use are iodine (^{131}I) and phosphorus (^{32}P). The body cells deal with these artificial radioactive isotopes in exactly the same manner as their naturally occurring non-active counterparts.

Radioactive iodine (^{131}I) *in the treatment of thyrotoxicosis.*—^{131}I, administered orally, offers a most satisfactory method of treating thyrotoxicosis, and the only factor which prevents this form of treatment from being universally accepted as the method of choice is the hypothetical risk of inducing malignant change in the thyroid gland. Many thousands of patients have now been treated by ^{131}I in various centres all over the world and to date no case of thyroid cancer has been reported. If there is any real risk at all it must be extremely small and after another few years elapse it is almost certain that ^{131}I will become generally accepted

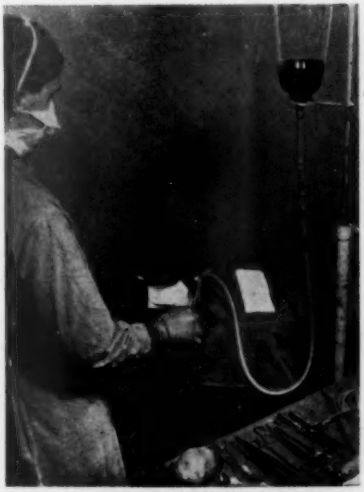

FIG. 10.—Intra-peritoneal insertion of radioactive colloidal gold for treatment of malignant peritoneal effusion.

FIG. 11.—Small superficial papillary tumour (x 25). When the whole bladder mucosa is involved by such lesions intracavitary irradiation offers a suitable method of treatment.

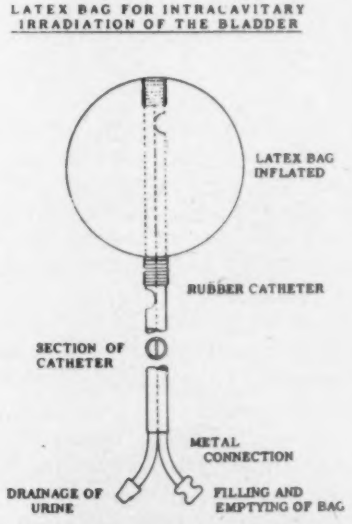

FIG. 12.—Balloon catheter for intracavitary irradiation, using radioactive bromine.

as the best method of treating thyrotoxicosis. At present a very conservative approach is generally recommended and ^{131}I is reserved for specially selected patients: e.g. those over the age of 45 years, those with recurrence of toxic symptoms following partial thyroidectomy (here the results of a second operation are poor and the risk of damage to the recurrent laryngeal nerves higher), and those in poor general condition, as in cases of advanced cardiac failure.

The radioactive iodine is given orally. On entering the blood stream the iodine is taken up by the thyroid gland in a highly selective manner, where it is used to form thyroxine. While concentrated in the gland, highly specific and localized irradiation of the thyroid takes place; this irradiation reduces the activity of the constituent cells and thus brings about a cure of the disease. Various schemes are used for estimating the dose required for any particular patient and the treatment may be given by means of a single dose or repeated smaller fractions. Some improvement in symptoms is often observed after four weeks, but the full benefit of treatment is not evident until three months have elapsed. If no benefit is observed from a single dose at the end of two months, it is unlikely that any further improvement will take place and the dose should be repeated.

Smooth hyperplastic toxic glands respond to much lower dosages than do nodular glands. Patients with severe toxic symptoms should first be brought under control by bed rest, sedation and antithyroid drugs, because in rare cases ^{131}I can precipitate a thyrotoxic crisis.

Following treatment by means of ^{131}I a small proportion (approximately 10 per cent.) of patients will become hypothyroid; in the majority of these patients this state is only of short duration (i.e. 'temporary post-^{131}I hypothyroidism'). The initiation of permanent myxœdema is at times purposely induced by ^{131}I in patients with severe anginal pain due to advanced cardiac disease; this brings about a general lowering of metabolic rate.

Iodine-131 in the treatment of carcinoma of the thyroid gland.—The initial hope that this isotope, by virtue of its highly selective uptake by the thyroid gland, would provide the answer to the treatment of thyroid cancer has not been realized. Generally speaking, only the more differentiated types of growth show worthwhile uptake of ^{131}I, and then always to a much smaller degree than normally functioning thyroid tissue. Hence it follows that in order to obtain maximum uptake of ^{131}I in malignant thyroid tissue as much normal thyroid as possible should be removed, and this may be accomplished by either surgical excision (the more rapid method) or administering a large dose of ^{131}I (ablation dose). About eight to ten weeks later a small tracer (1 mc.) dose of ^{131}I is given and its uptake is determined by external counting (fig. 13, 14). This is followed by a therapeutic dose (100 to 150 mc.) and this procedure is repeated at two- to six-monthly intervals. The uptake of iodine in malignant thyroid tissue may be increased by the administration of antithyroid drugs for a period of two weeks before giving a therapeutic dose; conversely, the administration of any iodine-containing medicine should never be given to such patients as it completely prevents the thyroid tissue from taking up iodine for many months.

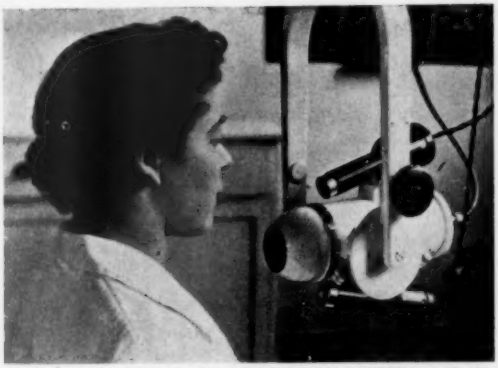

FIG. 13.—Estimation of radioactive iodine (^{131}I) uptake by thyroid gland by means of scintillation counter.

Radioactive phosphorus (^{32}P).—Treatment of polycythæmia vera by means of this isotope is now accepted as the method of choice. Patients with this disease have an increased blood volume and red cell mass and blood viscosity. Their numerous and distressing symptoms are due to these hæmodynamic abnormalities, which can be verified by blood volume studies using

red blood cells 'labelled' with radioactive chromium (^{51}Cr). These patients are best treated by 'dextran' replacement transfusion and simultaneous venesection, followed by the intravenous injection of radioactive phosphorus (approximately 5 to 7 mc.). The whole treatment can be completed in two to three days. Subsequent injections of ^{32}P are given as required. In this condition the hæmopoietic bone marrow is hyperplastic; it therefore readily takes up ^{32}P and the radiation thereby received reduces its activity.

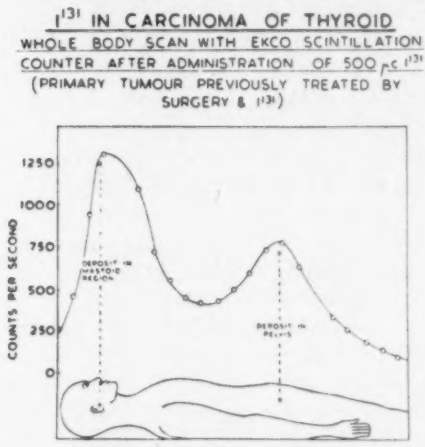

FIG. 14.—Carcinoma of thyroid: Detection of metastatic deposits by profile scan, using a scintillation counter.

Lymphosarcoma in its diffuse and generalized form, presenting as massive enlargement of many lymph glands, can be adequately treated by intravenous ^{32}P, which causes a dramatic reduction in the size of the nodes. Radioactive phosphorus is also often used in the treatment of chronic lymphatic and myelogenous leukæmia, by means of repeated small doses.

CONCLUSION

From this review it is obvious that artificial radioactive isotopes are an essential tool in the management of a large number of malignant processes. This therapeutic weapon is comparatively new and it is certain that it will be directed at many fresh targets in the near future.

I wish to express my gratitude to Professor D. W. Smithers, Director of the Radiotherapy Department, Royal Marsden Hospital, who initiated many of the techniques referred to in this article, to the staff of the isotope and photographic departments, and to Miss Johnson, for their cooperation.

A HOSPITAL RADIOACTIVE ISOTOPE UNIT

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With the expanding role of radioactive isotopes in diagnosis, treatment and research in modern medicine, it is apparent that facilities for their use will need to be available in an increasing number of hospitals, particularly in the investigation and treatment of thyroid disorders. At the present time these facilities are mainly restricted to teaching hospitals, and to a few of the larger non-teaching hospitals, but they will soon become a necessity in many more centres and they should certainly be available in towns with a population greater than 200,000, or less if situated some distance from a large centre. Relatively simple equipment is now available, supplies are easily obtained from the Atomic Energy Research Establishment, Harwell, and the Radiochemical Centre, Amersham, and the capital cost is not great in comparison, for example, with a diagnostic x-ray or radiotherapy department.

Radioactive isotopes may be needed in research by various departments of the hospital, but unless some special long-term project is involved it is better if the facilities are centralized in one laboratory. In this way the expert advice of a physicist is available for the constant supervision of techniques and equipment and the technicians can be thoroughly trained in the particular discipline of this type of work. It saves duplication of equipment and leads to more accurate results as many errors are unwittingly made by those unaccustomed to handling and measuring radioactive material.

SITUATION

The location of the laboratory within a hospital will no doubt depend upon the space that is available: it could be in an established general or chemical pathology laboratory, or it could be in, or adjacent to, a radiotherapy department. The latter is advisable as responsibility for treatment with radioactive isotopes rests with the radiotherapist and, as the assistance of a physicist is essential, use can often be made of the physics service already existing in most modern radiotherapy departments. Also there may be space already present for storing radium or radon seeds that could be expanded as a store-room for other radioactive isotopes.

One or more rooms are necessary for examining patients and measuring material; in addition, a separate room is needed to keep the isotopes, for preparing them in suitable form for administration and also for storing heavily contaminated excretions, particularly urine, before they can be

disposed of. There is, however, one serious objection to the siting of an isotope laboratory in a radiotherapy department, and that is the question of radioactive background, for the natural 'cosmic' background can be affected many fold by stray radiations from installations such as high-voltage x-ray or radiocobalt teletherapy units, if these be too near the counting equipment. Similarly the store-room must not be too near the 'counting house' or, if it is, it must be heavily screened.

PRECAUTIONS FOR PERSONNEL AND PATIENTS

It is unnecessary for technicians to wear special clothing when handling the small amounts of radioactive material used in tracer investigations for diagnosis or research and occasional therapeutic doses, as there is little danger from the effects of whole body radiation. It is a sensible precaution, however, for everyone to wear some form of film badge to check external exposure. The main danger is from direct contact of material on the hands and its subsequent possible ingestion. Consequently no smoking or eating is allowed while preparing samples. Rubber gloves should be worn when handling active material (>10 μc.) and at all times great care must be taken that no material is spilt on the hands. Some form of monitor should be available to check the possibility of contamination of hands if there has been any question of a spill and if significant radioactivity is detected they must be thoroughly washed and scrubbed.

Preparation of active material should be done behind lead screens; simple remote handling devices and piston-operated pipettes and the like should be available and used for all preparations above the microcurie level. For further details on this subject, the article by Fay (1952) should be consulted.

For patients receiving tracer doses for investigation no special precaution is necessary for themselves or the nursing staff. Urine is the most likely excretion to be radioactive and in most investigations this is collected for measurement. Patients undergoing treatment with radioactive iodine or phosphorus pass highly active urine for three or four days. They can be treated in an ordinary hospital ward, but should have their own marked crockery, and a bedpan should be kept for their sole use. Nurses should wear rubber gloves and aprons when handling the bedpans or contaminated sheets but, unless a large number of cases is being treated, no other special precautions are necessary. Patients should not be treated if there is a possibility that they may vomit the dose or if they be incontinent of urine. The urine can be kept in Winchester bottles on a balcony or similar site away from patients, from where it is collected by the staff of the laboratory every day and stored until it has decayed sufficiently to be disposed of down the sluice. Under present regulations the maximum amount that can be flushed down the normal sewage disposal system is 100 microcuries per flush or 1 millicurie per week. After an average therapeutic dose for thyrotoxicosis such urine has to be kept for two or three weeks; after an ablative

dose to destroy the gland it may have to be kept for as long as two months.

For the general run of patient treated no other precautions need be taken in the ward, either for the patients, their visitors or the nursing staff. By having patients in several wards it is most unlikely that any particular nurse will receive any significant radiation. If, however, many patients are treated in a special ward consideration must be given to whole body radiation that could be received by the nursing staff from frequent contact with many patients. They should wear a film badge and should be trained in the necessary discipline such as that advised for the laboratory technicians.

Should the patient be incontinent of urine or inadvertently spill urine, sheets and other contaminated bedding or clothing must be removed and kept apart until free from radioactivity. It is inadvisable to give therapeutic doses to any patient who is incontinent of urine or who has diarrhœa. Constant consideration has to be given to these precautions, for care is apt to lapse with familiarity and the whole subject should be reviewed once or twice a year.

EQUIPMENT

Laboratory benches or tables on which radioactive material is handled, either before administration to the patient or during preparation for counting, should be covered with some form of easily removable non-absorbable material such as polythene. This is easily changed if there is an accidental spill and it saves contamination of permanent woodwork. A simple Geiger-Müller monitor is required to check possible contamination of hands, clothing, benches and syringes, beakers, pipettes and the like used in the preparation of samples.

GEIGER-MÜLLER COUNTERS

Geiger-Müller counters have heretofore been the most widely used type of instrument for measuring radioactivity in medical work. Briefly, they consist of a gas-filled cylindrical vessel fitted with a pair of electrodes across which an electrical potential is applied. When the gas is ionized by radioactive material equal numbers of positively and negatively charged ions are formed which are attracted towards the oppositely charged electrode, resulting in a current through the circuit which can be measured and recorded electronically.

They are constructed in several forms: an 'end-window' type for measuring small quantities of dry material; 'liquid counters' for measuring fluids. They can be arranged in rings for detecting activity in large quantities of urine or stool or for estimating the uptake in the thyroid gland and indeed in many other forms for special needs. Fig. 1 illustrates three counters arranged in a triangle and fixed to a chair for the measurement of radioactivity in the thyroid gland following the administration of radioiodine (Langmead and Birchall, 1957).

Geiger-Müller counters are essential for measuring purely β-particle-emitting isotopes and they have the advantage that the background count

is very low. The chief disadvantages, compared with a scintillation counter, are: their poor efficiency for detecting γ-rays; the necessity to wash a liquid counter at least ten times between each specimen to be measured and the great care that has to be taken in the preparation of dried samples to see that the geometry of similar samples to be counted is the same.

SCINTILLATION COUNTERS

Scintillation counters are becoming more popular, as they are 10 to 20 times as efficient as a Geiger-Müller counter in the detection of γ-rays. A wide range of substances, called phosphors, have the property of emitting light from secondary electrons released by the impact of γ-rays. These minute scintillations are magnified in a photomultiplier tube and the resulting electrical pulses are then counted with electronic equipment. They are of no use for detecting β-particles and the other main disadvantage is the relatively high background count due to their high sensitivity for γ-rays.

FIG. 1.—Three Geiger-Müller counters arranged in a triangle and fixed to a chair for measuring thyroid uptake.

Two main types are in common use. A directional counter, which can be used for detecting γ-rays from a distance, which is of particular value for surface counting over the body; it can be used for measuring thyroid uptake, and for scanning the neck to determine, for instance, whether a nodule in the thyroid is 'hot' or 'cold'; or for determining whether a carcinoma of the thyroid will take up radioactive iodine. Such a role is illustrated in fig. 2, the counter in this instance being fixed to an automatic scanning device (Langmead and Birchall, 1957). They are also used for detecting activity in other organs, e.g. the heart, liver, spleen and bone marrow after administration of radioactive iron (Ledlie and Baxter, 1954; Wetherley-Mein *et al.*, 1956).

The other form commonly used is the 'well-type' counter which is particularly useful for measuring small samples of body fluids. Small glass cylindrical tubes (6 cm. high, 1.5 cm. in diameter, and 10 ml. capacity)

can be previously prepared with the samples which can then be counted successively by inserting the tubes into the 'well' without the necessity of repeated washings between each sample (*cf.* Geiger-Müller liquid counters). Very small amounts of radioactivity can be recorded by this means, though it must be re-emphasized that the background count is much higher than that of a Geiger-Müller counter and this may be a serious disadvantage.

It can be seen that there is now a wide variety of radiation detectors available according to particular needs. With the sort of counters mentioned many different types of investigation can be undertaken with most of the more frequently used radioactive isotopes, a notable exception being tritium for which special counting equipment is necessary. For further information on this subject the reader is referred to the article by Veall (1952).

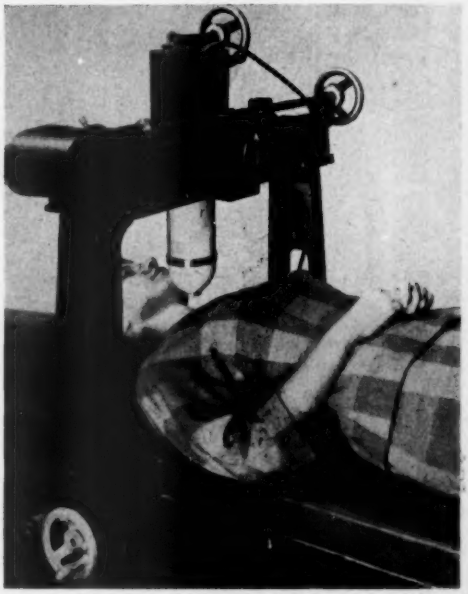

FIG. 2.—A directional scintillation counter incorporated in an automatic scanning device for mapping radioactivity in the thyroid.

ELECTRONIC RECORDING EQUIPMENT

Some form of electronic recording equipment is necessary to register the impulses received by the counters. These are of two main types, the scaler and ratemeter. A scaler records electronically the number of impulses received by a counter and registers them automatically. It can be relatively simple or extremely complex. Some of the more elaborate ones have a time signal incorporated, and can be set to record the number of impulses received in a prearranged time; alternatively they can be set to record the time taken for a prearranged number of impulses. The more simple ones have to be used with a stop-watch but, unless a great deal of counting has to be done, this is no great hardship and, as they have the merit of being simple, there is less to go wrong.

A ratemeter is used for samples containing more radioactivity, e.g. a 24-hour sample of urine after radioiodine. A dial is incorporated in the equipment and calibrated to record directly the number of impulses being received each second. This saves a lot of time, but it is of no value for counting low-activity samples. It is essential if some form of automatic

pen recording is needed such as may be used in the determination of cardiac output from external counting over the heart.

Various other forms of equipment, e.g. dose meter, pulse analyser and pulse generator, may be needed in larger laboratories, but these fall outside the scope of the present article.

ROLE OF A GENERAL RADIOACTIVE ISOTOPE LABORATORY

This can be illustrated by the work performed in the laboratory at St. Thomas's Hospital which is staffed by a physician, a physicist and two technicians, one of whom is primarily trained in chemical pathology. The main routine work performed concerns the investigation of thyroid disorders with radioiodine of which an average of 10 cases are seen weekly. Other investigations, both for diagnosis and research, have included the use of isotopes of sodium, potassium, bromine, and chromium; vitamin B_{12} labelled by biosynthesis with radioactive cobalt; and human serum albumin labelled with radioiodine. The latter has been used for estimation of plasma volume, for measurement of cardiac output, and for the study of albumin degradation in obscure forms of hypoproteinæmia. In 1956, 97 separate investigations were performed with these isotopes.

In collaboration with the radiotherapy department treatment is undertaken with radioactive iodine, phosphorus and colloidal gold. In 1956, 36 cases of thyrotoxicosis were treated; the thyroid has been ablated to induce myxœdema in six cases of chronic congestive failure, and eight cases of carcinoma of the thyroid have been investigated with a view to treatment. There were four cases of polycythæmia rubra vera, and in eight cases radioactive colloidal gold has been introduced into the pleura or peritoneum for the management of recurrent malignant effusions.

WHAT IT ENTAILS FOR THE PATIENT

Investigation and treatment of patients with radioactive isotopes are relatively simple and far less unpleasant than many of the accepted lines of investigation in other spheres. Diagnostic procedures may be performed on outpatients, but when treatment is undertaken patients must be admitted and they should be kept in hospital until the amount of radioactivity present in them has fallen to 5 mc.

The isotopes are usually administered by mouth or intravenously, although occasionally they may be given by other routes: e.g. subcutaneously for measuring clearance of radioactive sodium from the skin of a pedicle graft. Those given by mouth are normally in aqueous solution and are quite tasteless. Patients, being human, often complain later that they felt sick or more nervous after administration, but as often they state that they felt much better and date the onset of their improvement from the time when the dose was given; this is all due to suggestion and the more phlegmatic patients notice no effects. A great deal can be done by simple explanation beforehand. X-ray diagnostic procedures and 'blood tests' are accepted

by patients as necessary evils and cause few qualms even though they may give considerable discomfort. Radioactive investigations, on the other hand, are new and it is understandable that there should be considerable apprehension.

External measurements with counters, either over the thyroid gland or other sites, cause no discomfort at all, though the patient may be required to lie still for half an hour. Neither is there any discomfort from the collection of urine although there may be some inconvenience, particularly for outpatients. After adequate explanation it is found quite satisfactory to have outpatients collect their urine and bring it back to the laboratory; in fact it is a general experience that these outpatient collections are far more likely to be accurate than those made in a busy general ward. Samples of blood or plasma may have to be taken and occasionally of other body fluids: e.g. pleural or peritoneal, but these are no more unpleasant to the patient than biochemical or hæmatological investigations and seldom will as many pricks be necessary as in a glucose tolerance curve.

Similar remarks apply to the therapeutic use of radioactive isotopes. For thyrotoxicosis one drink of a tasteless fluid containing radioiodine is given which causes no side-effects; for polycythæmia vera one injection of radioactive phosphorus, though both of these may have to be repeated later. The administration of radioactive colloidal gold into the pleural or peritoneal cavities should cause no more discomfort than the original removal of the fluid, although in this case there may be some anorexia and nausea for one or two days similar to that after conventional deep x-ray therapy.

In fact, one of the great advantages of these new techniques is their simplicity and the little disturbance they cause to the patient. Once the equipment and knowledge are available the relative ease and accuracy of the measurements make the use of radioactive isotopes a comparatively simple means of investigation. They will seldom supplant established methods in diagnosis, but they have already helped in the solution of many problems and it seems likely that many more uses will be found in diagnosis and research and, it is to be hoped, in treatment too.

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RADIOGRAPHY WITH RADIOACTIVE ISOTOPES

By H. J. D. IRELAND, B.Sc.

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The naturally occurring radioactive materials such as radium have been used as radiographic sources from the earliest days of their discovery at the end of the nineteenth century. Since that time many industrial uses have been found for these x-ray emitters, as, for example, the detection of blow-holes and other flaws in metal castings.

In the field of medicine, however, the high penetrating power of these natural x-ray sources is far too great for radiography of the human body, both soft tissue and bone being traversed with almost equal facility. As a result of this no useful degree of contrast is registered on the photographic film. This situation, however, has been changed by the rapid post-war development of atomic physics, which has, amongst its many other achievements, made available a large number of artificial sources of x-radiation. Of these radioactive isotopes a few have penetrating powers low enough to produce satisfactory contrast as between bone and tissue.

Using one of these isotopes it is now possible to produce an extremely simple x-ray apparatus of such small weight and size that it can be carried around, together with a supply of films and cassettes, in a container little larger than a normal brief case. The apparatus is completely self-contained and requires no external power either from electricity mains or batteries. The possibilities of such an apparatus are many and varied. In field work, both military and civil, uses will at once come to mind, especially the examination of casualties. In the veterinary world also this type of apparatus may be of considerable value due to the ease with which it can be handled. Other uses already found include the radiography of old paintings and of porcelain figures.

To extend the usefulness of such an apparatus a portable film-developing outfit would be of great value and already a process has been developed by Picker-Polaroid, which has considerable possibilities in this field.

CHOICE OF SUITABLE ISOTOPES

We have seen that the primary requirement of a radioactive isotope for medical use is that its energy should be low enough to give good contrast; energies in the region of 50 kV have been found to be suitable. A secondary requirement is that the isotope should have a reasonably long half-life in order to avoid frequent replacement and recalculations of dose-rate as its strength decays. Two isotopes in particular have been investigated which

to a large extent fulfil these conditions: thulium-170 and xenon-133.

Thulium-170 is prepared from normal non-radioactive thulium-169 by placing it in the strongest available neutron flux of an atomic pile. The radioactive isotope is formed by neutron capture and proceeds to decay with a half-life of 127 days.

The decay scheme is complex (Mayneord, 1952; Mayneord and Ireland, 1956; Lidén and Starfelt, 1953) but, briefly, is by β-emission by two routes, one to stable ytterbium and the other to an excited state of ytterbium which emits γ-radiation of 84 kV and also its own characteristic x-radiation of 52 kV and 59.4 kV by a process known as internal conversion. In addition, there is a continuous broad band of bremsstrahlung radiation with a mean energy of about 150 kV. This is caused by the deceleration of the β-rays in the thulium, the mechanism being very similar to the production of x-rays in a normal x-ray tube.

Xenon-133, a gas, is a fission by-product of pile operation, it occurs in large quantities and has to be extracted by chemical and physical processes (Richards, 1955).

The decay scheme (Bergstrom, 1951) is by β-emission to cæsium-133 which emits a γ-ray of 81 kV; this is internally converted and gives rise to x-radiation of 31 kV and 35 kV. No bremsstrahlung is present in the radiation from xenon-133.

For radiographic purposes it is well understood that for the highest definition we must have as near a point source as possible; this necessarily implies a high concentration of activity if the times of exposure are not to be excessive.

In the case of thulium-170 it has been possible to irradiate a disc of sintered thulium oxide, 2 mm. in diameter and 2 mm. thick, and reach an activity of several curies with dose-rates of up to 3 mr/minute at 30 cm. To prevent leakage of the active material and to absorb the unwanted β-rays the active disc is sealed into a light alloy capsule which is itself sealed into a second capsule, the total thickness of alloy being about 2.25 mm.

Xenon-133 radioactive sources are prepared by absorption of the gas on to charcoal at the temperature of liquid nitrogen (Richards, 1955); on reaching normal room temperatures it is found that most of the gas remains strongly absorbed.

Activities of one to two curies have been concentrated in charcoal grains of about 1.5 mm. in diameter. Sources of up to 13 curies have been made by absorbing the gas in a charcoal rod 1 mm. in diameter by 5 mm. long. The rod is sealed in a glass capillary tube and is viewed end-on in order to achieve small focal size. Such sources give dose-rates of up to 75 mr/minute at 30 cm.

APPARATUS FOR CLINICAL USE

For practical purposes the primary sources described above must be shielded and a suitable shutter mechanism arranged so that exposures can be made when required. The shielding must be adequate, so that when the shutter is closed the source is safe to handle; due to the low energy of the sources this is easy to attain. For both the thulium-170 and xenon-133 sources, of the above orders of magnitude, 0.6 cm. of lead is sufficient to reduce the dose-rate to less than the maximum permissible of 2 mr/hour at one foot from the source. Theoretically the best absorber is gold, especially of radiations in the region of 80 to 100 kV (Mayneord, 1952; Mayneord and

Ireland, 1956); as little as 3 mm. of this material is sufficient for shielding purposes when the source strength does not greatly exceed the above figures.

It will be obvious that there are many simple methods of making a suitable shutter, the precise approach depending on the application in mind. One solution, designed for clinical use, is illustrated in fig. 1. It was originally intended to contain the double-sealed thulium-170 disc but it can easily be adapted to hold xenon-133 sources.

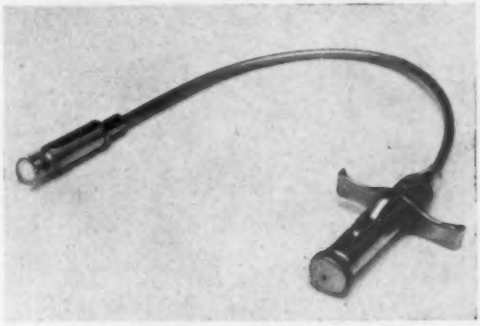


FIG. 1.—Gold-shielded clinical source holder.

The dual capsule holding the thulium is connected to a Bowden cable leading to the operating plunger, the cable length being about 25 cm. The far end of the capsule is covered by a gold disc, 3 mm. thick, which in the closed position lies within the end of a gold cylinder of 3 mm. wall thickness. This gold cylinder is terminated by a perspex dome into which the capsule and its gold disc move when the plunger is operated. This is the exposed position and it will be seen that a 'lighthouse' beam or, more precisely, disc of radiation is emitted.

A possible application for this type of source holder is internal radiography, the source being inserted into various body cavities with the film outside. In this way unusual views can be taken, one advantage being that the normal superimposition of structures is avoided. Difficulties arise, however, in that the source, due to its close proximity to body tissue, causes a very high surface dose-rate: for example, the dose-rate due to a particular xenon-133 source was 250 r/minute at 0.5 cm. Another problem lies in the fact that because of the short focal distances involved there will be considerable geometrical distortion.

FIG. 2.—Gold-shielded clinical source holder on demountable stand, and cassette holder.

For normal use this source holder can be mounted on a stand such as that shown in fig. 2. This allows for variation of source-film distance and by sliding the source along the horizontal arm it can be centred over cassettes of various sizes. The illustration shows a 12 inch (30.5 cm.) × 10 inch (25 cm.) cassette in position. The whole stand is

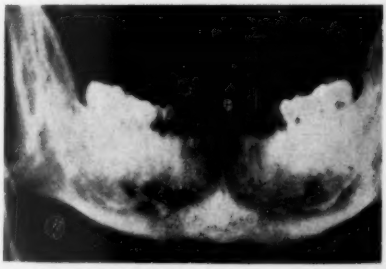
demountable and packs into a comparatively small space for transportation.

RADIOGRAPHIC EXPERIMENTS

The dose-rate from sources at present available does not approach that produced by conventional x-ray apparatus. As a result, we must use shorter focal distances and longer exposure times than in normal practice. To reduce the time of exposure to the minimum, fast films and intensifying screens are necessary and for this purpose we have used Ilford double-coated 'red seal' films and Ilford H.V. screens. For the type of work on which these sources are likely to be used the results are very satisfactory despite the loss of definition inherent in this combination of films and screens. A stationary Lysholm grid was tested with various objects but no improved definition could be demonstrated and the exposure times were doubled. A moving Bucky diaphragm resulted in a slight improvement but again at the expense of increased times of exposure.

We have seen that thulium-170 sources have a bremsstrahlung component with a mean energy of about 150 kV. This comparatively hard radiation results in a noticeable loss of contrast; in this respect thulium-170 compares unfavourably with xenon-133 which has no significant radiation above 85kV. As the amount of bremsstrahlung present is directly related to the volume of thulium in the source, we should expect a small fragment of thulium-170 to give very much better con-

FIG. 3.—Radiograph of mandible of dried skull taken with a fragment of thulium-170 in mouth.



(a)

(b)

FIG. 4.—Mandible. Comparison of (a) x-ray and (b) thulium-170 radiographs.

trast than larger sources. That this is so can be seen by comparing the radiograph in fig. 3, taken with a small fragment, with that in fig. 4 (b), taken with a 2-mm. disc source. It is unfortunate that fragmentary sources

(a) (b)

FIG. 5.—Xenon radiographs: (a) normal ankle, (b) fractured ankle.

(a) (b)

FIG. 6.—Xenon radiographs: (a) hand, exposure 3 seconds; (b) elbow, exposure 8 seconds.

cannot be produced with sufficient strength to give short exposure times; the radiograph of fig. 3 required an exposure of about 10 hours.

The presence of bremsstrahlung, together with the fact that thulium-170 is not such a safe material to handle, has led to the conclusion that xenon-133 is a more satisfactory source. Its disadvantage of a short half-life of 5.27 days can be set against the fact that due to the very large amounts available in atomic reactors it should be a simple matter to arrange for a supply of replacement sources at low cost. Some examples of radiographs made with xenon-133 are shown in fig. 5 and 6. The source used had an initial dose-rate of 70 mr/minute at 30 cm., this being the source-film distance at which most of these pictures were taken. It will be seen that radiography of the extremities is possible with exposures as short as 3 seconds when sources of this magnitude are employed. The radiograph in fig. 7 is included as one example of the many non-medical uses for these radioisotope sources.

FIG. 7.—Radiograph of porcelain ornament taken with a fragment of thulium-170.

A useful application would be in dental radiography, the method being to place the radioactive source in the centre of the mouth with the film wrapped round the outside of the face. Advantages would be orthogonal views of the full complement of teeth at one exposure instead of the many separate exposures required when using normal techniques. The source-film distances are of course very small, and this results in geometrical distortion from two causes; one due to the thickness of the teeth and the other to the finite size of the source. With sources of 2 mm. diameter the results have so far not been satisfactory but it is hoped that with a reduction to 0.5 mm. or less some useful results may be obtained. In this case the unavoidable reduction of source strength with size is offset by the short source-film distances.

A comparison of fig. 4 (a) and 4 (b), both of which were made with the same geometrical conditions and films, will make clear the difference in quality between thulium-170 and normal x-ray tube radiations. This difference is probably due to the continuous nature of the tube spectrum as compared with the mainly monochromatic line structure of the thulium-170. Here we may note that an x-ray tube at, say, 75 kV has an effective

average radiation energy considerably above this, in the region of 100 to 120 kV. Nevertheless, in spite of this poorer quality, radioactive isotopes, whilst not suitable for fine detail examination, have shown that for gross changes, e.g. dislocations and fractures, they may have a useful role to play in human radiography.

HAZARDS

We have seen that the radiation from these isotopes is easily screened and reduced to a safe level. There is, however, a serious risk from accidental ingestion of the active material. Thulium-170 is generally produced from sintered thulium oxide so that the possibility of some of the powder escaping from its capsules must be guarded against. Thulium-170 is a bone-seeker with an effective biological half-life of 60 days, the maximum safe body burden is only 4 microcuries (recommendations of the International Commission on Radiological Protection, 1955). This amounts to less than 0.1 micrograms of the material, underlining the need for perfect sealing. From this point of view it would be better to use the metal instead of its oxide (Untermyer *et al.*, 1954).

Xenon-133 is less dangerous because of its short half-life, the maximum permissible air concentration is 4×10^{-6} microcuries/ml. and the maximum body burden is 320 microcuries (Tobias *et al.*, 1949). A further safeguard is the fact that, in common with the other rare gases, it is chemically inert and not easily absorbed in the body.

This account is possible due to the early interest taken in the subject by Professor W. V. Mayneord, the director of the department of physics, and to the work he has devoted to the subject in the last few years. The sources have been made available due to the kindness of many friends in the British and Canadian Atomic Energy Establishments. Dr. M. W. Wood of the x-ray diagnostic department of the Royal Marsden Hospital has given great assistance in the clinical aspects of the work.

Figures 1, 2, 4, 5 and 6 are reproduced from the *British Journal of Radiology*, and figure 3 from *The Lancet*, by kind permission of the Editors.

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THE PHYSICAL BASIS OF HEADACHE

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'I shall therefore commend to you the study of symptoms for their own sake as well as for the sake of your patients and your professional reputations'.—J. A. Ryle (1936).

HEADACHE is one of the most common symptoms encountered in clinical medicine, and one of the most troublesome. It is therefore a little surprising that it is almost ignored in medical teaching and writing in this country; the more so because much has been learned about it in the last two decades, and there is now a considerable body of established anatomical and physiological facts relating to it, much of which is of practical value and interest to the clinician. This article is an attempt to outline this knowledge and to indicate its clinical relevance.

PAIN

Headache is essentially pain in the head, and some knowledge of the physiology of pain and the anatomy of the head are essential to a proper understanding of it.

Pain is a subjective sensation which evades definition: let it suffice to say with Lewis (1942) that it 'is known to us by experience and described by illustration'. It is a specific and independent modality of sensation like heat, cold and touch (Adrian, Cattell and Hoagland, 1931). Pain receptors are plain bare nerve-fibrils; in the skin they are excited by a wide variety of stimuli such as pricking, cutting, burning, pinching, and the application of caustic chemicals, but in other tissues the range of noxious stimuli is smaller; for instance, the intestinal wall probably responds only to stretching and ischæmia (though the evidence on this point is not wholly conclusive [Kinsella, 1948]). Skin, as befits its protective function, is liberally provided with pain receptors, but deeper tissues have fewer, and some, such as the brain and bone marrow, none at all.

Pain arising in the skin is well localized, promptly felt, and has a quality described as pricking or burning: that arising from deeper structures is less well localized, less urgent, and is described as dull, aching or throbbing; it tends to give rise to false localization by reference, spread and muscle spasm, and to evoke autonomic accompaniments such as sweating, bradycardia, and nausea (Lewis, 1942).

Pain impulses from the skin (and probably elsewhere) reach the central nervous system via two sorts of fibres: some thin and poorly myelinated with a slow rate of conduction, others thicker and well-myelinated with a rate of conduction about twenty times as great (Bigelow *et al.*, 1945; Gasser, 1934). It is of some interest that those impulses which originate nocifensor reflexes (such as the instantaneous withdrawal of an injured limb, before the hurt is properly appreciated by consciousness)

travel by the thicker, more rapidly conducting fibres, and it is these that are chiefly damaged in a disease such as tabes dorsalis.

Pain-fibres of both sorts enter the spinal cord by the posterior root and relay in the grey matter of the posterior horn (and also communicate with neurons in neighbouring segments, especially those cephalad); second-stage fibres cross the cord to ascend in the lateral spino-thalamic tract to the posterior ventral nucleus of the thalamus. At this point the sensation of pain

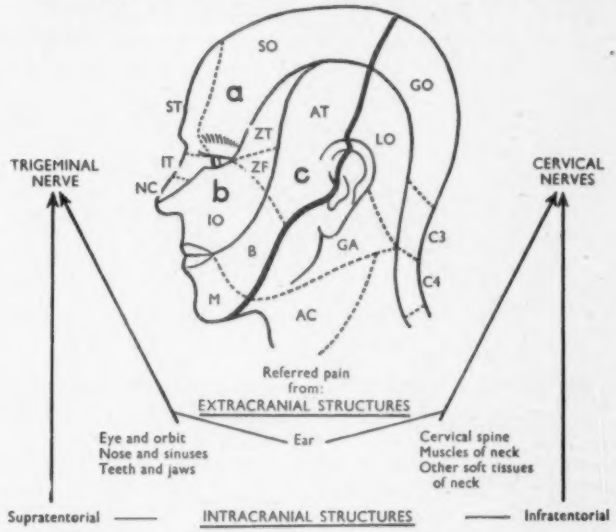

FIG. 1.—Cutaneous innervation of the head, and main areas of reference of pain arising in deeper structures.

Abbreviations:

a . . . 1st (ophthalmic) division of trigeminal nerve.
b . . . 2nd (maxillary) ,, ,, ,, ,,
c . . . 3rd (mandibular) ,, ,, ,, ,,

Branches of trigeminal:

a: supraorbital (SO), supratrochlear (ST), infratrochlear (IT), nasociliary (NC).
b: zygomaticotemporal (ZT), zygomaticofacial (ZF), infraorbital (IO).
c: auriculotemporal (AT), buccal (B), mental (M).

Branches of cervical nerves:

anterior primary rami: lesser occipital (LO), great auricular (GA), anterior cutaneous of neck (AC) (all from C_{2-3});
posterior primary rami: greater occipital (GO), and P.P.R. of C_3, C_4, etc. (GO from C_2).

enters consciousness, but there are intimate connexions between the thalamus and postcentral convolutions of the cortex, described by Walker (1943); these probably serve to amplify the basic thalamic pain-sensation and coordinate it with other afferent stimuli, and also to modify the primitive thalamic responses to pain such as the 'sham rage' and 'sham grief' seen in decorticate animals and occasionally in human patients with lesions in the thalamic region (Cannon, 1929; Goltz, 1892).

Pain-fibres from the trigeminal nerves relay in the spinal or descending

root of the nerve, those from the ophthalmic division in the lowest part, the maxillary in the intermediate part, the mandibular in the uppermost; second-stage fibres then cross to the other side of the brain-stem to ascend in the thalamus in close company with the spino-thalamic fibres.

NEUROLOGY OF THE HEAD

Table I shows that, whilst most extracranial structures are pain sensitive in varying degrees, this is not true of the cranium itself or its contents. It is noteworthy that the brain and much of the meninges are insensitive, and

Sensitive to pain	Insensitive to pain
EXTRACRANIAL	
Skin	Superficial veins
Subcutaneous tissue	Cranial bones
Muscles, tendons, aponeuroses	Diploë
Arteries	
Nerves (usually)	
Orbital contents	
Mucosæ of oronasal cavities, middle ear, etc.	
Periosteum, pericranium	
Teeth, jaws	
INTRACRANIAL	
Dural floor of anterior and posterior fossæ	Dura of vault, floor of middle fossa, falx, tentorium
Dural venous sinuses, and dura in their immediate vicinity	Pia-arachnoid
Large arteries at base of brain, and their larger branches for a variable distance from their origin	Ependyma
	Choroid plexuses
	All other blood vessels
Meningeal arteries, and dura in their immediate vicinity	Other cranial nerves
Cranial nerves V, VII, IX, X, XI, XII	Parenchyma of brain

TABLE I.—Pain-sensitivity of structures and tissues of the head. No attempt is made to indicate degrees of sensitivity. This table is based for the most part on data from Wolff (1948), supplemented from many other sources.

by far the most important intracranial pain-sensitive structures are the larger blood vessels and the dura in their immediate vicinity.

Figure 1 shows the superficial sensory innervation of the head, and also indicates in a broad way the areas to which pain is referred from various intra- and extra-cranial sites. It will be seen that the trigeminal nerves are responsible for most of the head anterior to the ears, and the supratentorial cranial contents; the posterior part of the head is innervated by the second and third cervical nerves, and infratentorial structures by the last four cranial and first three cervical nerves.

REFERRED PAIN

Pain caused by noxious stimulation, especially of a deep structure, is often felt in another region of the body whose sensory innervation is derived from the same segment (Lewis, 1942). Although the precise mechanism of pain

reference is still a matter of controversy, clinical examples are legion: for instance, pain in the shoulder in diaphragmatic pleurisy (both regions being innervated by the fourth cervical segment, via branches of the cervical plexus and the phrenic nerve, respectively).

Referred pain plays an important part in headache, and most if not all headache from intracranial causes is referred. Wolff (1948) and others have

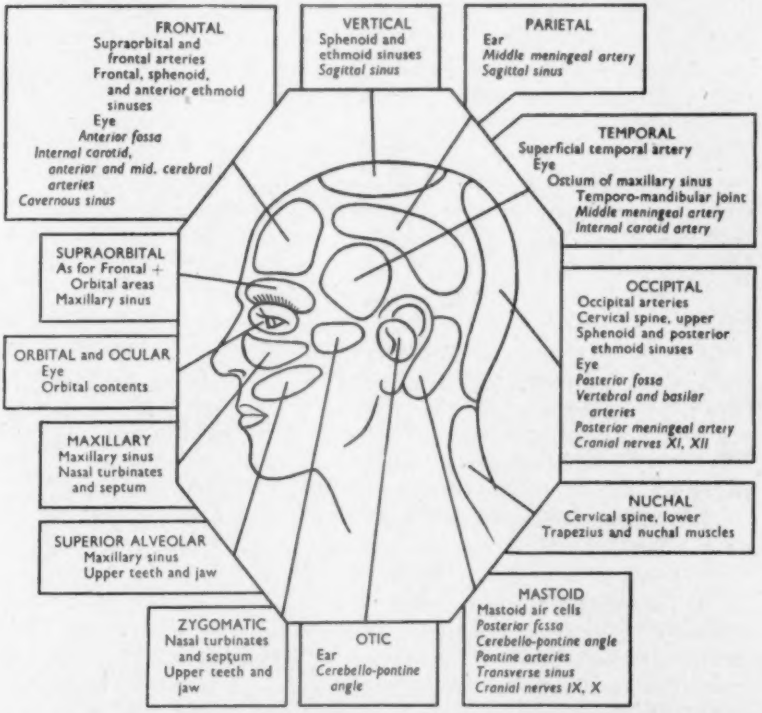

FIG. 2.—Approximate areas of reference of pain arising in some of the more important intracranial and extracranial situations. Intracranial structures are designated by italics.

worked out with much ingenuity the areas of reference of pain arising in a great number of intra- and extra-cranial situations, some of the more important of which are shown in figure 2.

SPREAD OF PAIN

Kunkle and Armistead (1948) showed that if the middle finger is immersed in ice-cold water it becomes painful, and that after a while the pain appears to spread to the adjacent fingers: this spread is neither prevented nor relieved by local anæsthesia of the adjacent fingers, because it is central and not peripheral in origin. The persistent flow of afferent stimuli into neurons

concerned with pain sensation in the immersed finger 'overflows', so to speak, via communicating fibres of the dorsal horn and association fibres in the white matter of the cord to neighbouring neurons in the same and adjacent segments. This central diffusion is especially important in pain arising from deep structures, and plays a considerable part in the production of headache in disorders of extracranial structures such as the eyes, sinuses and teeth.

PAIN OF MUSCULAR ORIGIN

Lewis and Kellgren (Lewis, 1942) showed that persistent noxious stimulation of a structure causes tonic contraction of muscles innervated from the same segment, with pain and tenderness in the muscles in due course. The phenomenon is familiar enough in the fixation of a painful joint, or the rigidity of the abdominal wall over a patch of peritonitis. It is somewhat less familiar in the form of temporal pain and tenderness from spasm of the temporalis muscle in disease of the temporo-mandibular joint, parotitis, or malocclusion; or occipital headache associated with disease of the upper cervical spine, or posterior cervical lymphadenitis. Spasm of the muscles of the scalp and forehead, the nape, the temple, the sternomastoid and ocular muscles, may in fact be provoked by a wide variety of painful conditions about the head and neck: for example, ocular disease, neuralgia, toothache, sinusitis, lymphadenitis, cervical spine disease, meningeal irritation, and the effects of trauma. In addition, headache from any cause, such as migraine, may be intensified, spread and prolonged by reflex muscle spasm.

Painful spasm may also be brought about by disorders of the muscles themselves, the commonest being muscular rheumatism (or 'fibrositis'), a frequent cause of mild, persistent headache, especially in the occipito-nuchal region. Auerbach, in 1913, emphasized the importance of this form of headache, yet even today it is commonly overlooked.

The typical headache of emotional tension is largely or entirely muscular in origin, and Sainsbury and Gibson (1954) have shown electromyographically that the onset of such a tension headache is accompanied by an increase in electrical activity of the scalp muscles. Wolff (1948) considers that the persistent deep suboccipital ache so common in hypertension is also muscular. Postural or occupational headaches in typists, car-drivers and others are further examples of entirely or predominantly muscular headaches.

Simons and Wolff (1946) demonstrated that many chronic post-traumatic headaches are of muscular origin; they may be localized to the traumatized area or scar, or generalized, but in either case demonstrate the general clinical features of muscular headache, which are:—

(1) Low to moderate intensity, often a feeling of pressure or vague discomfort rather than pain.

(2) Persistence, opposed to the paroxysmal nature of most vascular headaches.

(3) Clinically detectable spasm and tenderness of the involved muscle masses, with aggravation of the headache by firm palpation of these or of 'trigger points' therein.

(4) Electromyographic evidence of increased activity in the affected muscles.

(5) Relief, perhaps only temporary, following the abolition of spasm with the aid of physiotherapy, muscle relaxants such as mephenesin, or infiltration with procaine.

ARTERIAL HEADACHE

When a normal person is given an injection of histamine, after a brief interval he experiences a throbbing headache lasting a few minutes. This histamine headache has been carefully studied by Pickering and Hess (1933) and others, and has the following important characteristics:

(1) It is relieved by lowering the blood pressure in the branches of the internal carotid artery (e.g. pressure on the internal or common carotid in the neck); or raising the cerebrospinal fluid pressure (e.g. intrathecal injection of fluid, or pressure on the internal jugular vein).

(2) It is aggravated by procedures having the opposite effects (e.g. coughing, straining, and withdrawal of cerebrospinal fluid); and by shaking or jolting the head.

(3) The throbbing of the pain is synchronous with the carotid pulse.

(4) At craniotomy the headache is seen to be accompanied by dilatation and increased amplitude of pulsation of the cerebral (but not meningeal nor extracranial) arteries.

(5) The headache is most severe when the blood pressure has returned to near normal after its preliminary fall, but the cerebral arteries are still hypotonic and dilated.

These and other observations indicate that the headache is caused by stretching of periarterial nerve plexuses of cerebral arteries through excessive amplitude of pulsation: or, to put it another way, by the shock of systole impinging upon a hypotonic and imperfectly supported arterial wall.

There is evidence that the headaches of fever, the alcoholic hangover, anoxia, concussion, and that produced by vasodilators such as the nitrites, are similar in mechanism to the histamine headache; a related variety is that which occurs with a sudden lowering of cerebral arterial blood pressure from such a cause as the rapid assumption of the upright posture in certain predisposed persons (Kunkle, Lund and Maher, 1948; Marmion, 1956).

Migraine, in contrast to histamine headache, is for the most part a disorder of the external carotid system of arteries. The temporal, or sometimes the occipital, artery on the affected side can indeed be seen to be dilated and pulsating forcibly during an attack, the pain being relieved by partly occluding the artery by digital pressure near its origin, or by pressure on the external carotid in the neck; but if the attack persists for long the arterial wall becomes œdematous and these procedures bring little or no relief. Intracranial vessels are also involved in migraine, for the aura is caused by constriction of cerebral vessels and may be terminated by prompt inhalation of amyl nitrite (Shumacher and Wolff, 1941). Moreover, there is evidence that in some cases at least intracranial arteries are partly responsible for the pain. Ergotamine is a powerful constrictor of branches of the external carotid system, and this accounts for its efficacy in relieving the migraine headache, as demonstrated by Lennox and von Storch (1935); alone or in combination with caffeine it will abort or greatly relieve over 80 per cent. of cases.

Sutherland and Wolff (1940) have shown that the common headache of

arterial hypertension (but not that of hypertensive encephalopathy) resembles migraine in its causation. Many of the so-called 'atypical facial neuralgias' (Campbell and Lloyd, 1954), including Horton's histamine cephalalgia (Horton, 1940) and Sluder's 'lower-half headache' (Sluder, 1908), are also nowadays considered to be autonomic and vasomotor disturbances related to migraine. A large number of common everyday headaches are of arterial origin, both intra- and extra-cranial vessels being involved in varying degrees.

The foregoing types of arterial headache may be considered physiological because the arterial changes are brought about by physiological agencies and are ephemeral and reversible: in contrast are arterial headaches due to irreversible, permanent or progressive changes such as aneurysms, angiomas, arteritis and degenerative conditions. It would take too long to discuss these here, and the interested reader is referred to standard up-to-date neurological textbooks and monographs.

INTRACRANIAL SPACE-OCCUPYING LESIONS

In 1913, referring to the headache of cerebral tumour, Auerbach said: 'There can be no doubt that it is the pressure [of cerebrospinal fluid] as such which produces a powerful irritation of the nerves of the dura mater'. Thirty-five years later, Wolff and Wolf (1948), writing on the same topic, could say that 'increased intracranial pressure is neither a prime nor an essential factor'. It has in fact been well established that pain occurs only when the lesion directly or indirectly causes displacement or distortion of the larger blood vessels or other pain-sensitive structures within the skull (Ray and Wolff, 1940). This explains why greatly raised intracranial pressure can be present without headache, whilst a small tumour or aneurysm causing little or no increase in pressure can, nevertheless, give rise to severe headache. Furthermore, a leak of cerebrospinal fluid (with a *decrease* in pressure) after lumbar puncture can permit a slight but massive displacement of the whole of the cranial contents with consequent traction upon their pain-sensitive anchorages, causing severe headache.

These facts also indicate why the site of the pain is often of poor localizing value in intracranial tumour, since the structure whose distortion causes pain may well be at some distance from the tumour, even in a different cranial fossa or on the opposite side; for the distortion may not be due to the tumour mass itself, but to œdema or ventricular distension caused by interference with the circulation of blood or cerebrospinal fluid. Nevertheless, Wolff and Wolf (1948) make some helpful generalizations about the localizing value of headache in tumour:—

(1) In the absence of papillœdema, if the headache is unilateral it is likely to be on the side of the tumour.

(2) Pain initially or entirely at the back of the head indicates a posterior fossa tumour.

(3) In the absence of papillœdema headache in the front of the head suggests a supratentorial tumour.

(4) If headache is both frontal and occipital it is of little localizing value.

(5) The situation of headache in the earlier stages of the history may be of localizing value, when in the later stages the headache has become more diffuse.

HEADACHE DUE TO MENINGEAL IRRITATION

The meninges are sensitive to irritation by infection and by foreign substances such as blood and air. Examples of headache from these causes are those of meningitis, subarachnoid hæmorrhage, and pneumencephalography, respectively. It is apt to be severe and accompanied by symptoms and signs which are generally recognized as indicative of meningeal irritation: to wit photophobia, irritability, restlessness, nuchal muscle spasm and head retraction, nausea and vomiting.

NEURALGIA, NEURITIS AND NEUROGENIC PAIN

The common neuralgias, such as trigeminal and glossopharyngeal, do not give rise to true headache except by provoking secondary muscle spasm.

Any nerve may be the seat of neuritis from a variety of causes, and neuritis of the supraorbital, occipital, and auriculotemporal nerves, for example, may cause headache both of itself and through reflex muscle spasm. Infection of the posterior root ganglia (and their cranial homologues, especially the Gasserian and geniculate ganglia), as in herpes zoster and tabes dorsalis, also causes pain of neuritic character; post-herpetic neuralgia in various situations about the head is not uncommon in the elderly.

Pressure upon nerves or roots may cause pain, as in the occipital headache that may be caused by orthopædic conditions of the upper cervical spine; whilst the divisions of the trigeminal nerve are especially apt to be affected by aneurysms and other masses in the neighbourhood of the cavernous sinus. A neurofibroma in the course of a nerve of the scalp is an occasional cause of headache.

Disorders of the pain pathways, the spino-thalamic and quinto-thalamic tracts and the thalamus, must be mentioned for completeness, but are rarely causes of headache.

HEADACHE OF PSYCHOLOGICAL ORIGIN

Headache of psychological origin is one of the commonest conditions in medicine: it is an almost invariable symptom of anxiety neurosis and tension states, it is common in hysteria, depression, and psychopathic personality, and also occurs in obsessional states, schizophrenia, and many organic dementias.

Muscular tension headache has already been considered, and may be regarded as a by-product of the increased muscle tone that is part of the instinctive reaction to danger and stress. Vascular headache of emotional origin is probably equally common, but less easily explained, although a simple pressor headache may be caused in some persons by the release of adrenaline at times of stress. Cannon (1929) showed how emotions such as

fear and rage, acting on autonomic centres in the hypothalamus, prepare the body for violent activity—'fight or flight'—by, amongst other adjustments, vasomotor changes bringing about redistribution of blood; he also observed that 'if no action succeeds the excitement, and the emotional stress . . . persists, then the bodily changes due to the stress are not a preparatory

Mechanism	Physiology	Familiar clinical example	Example of headache
Direct	Pain felt at site of noxious stimulus.	Pain of pricked finger felt at site of prick.	Temporal headache in temporal arteritis.
Referred	Pain referred from site of noxious stimulation to another site of similar segmental innervation.	Pain in the shoulder in diaphragmatic pleurisy (both C4).	Supraorbital headache in internal carotid aneurysm (both trigeminal).
Spread	Noxious stimulus causes excitation of sensory neurons in posterior horn with 'overflow' of excitation to other neurons in same and neighbouring segments, so that pain appears to spread to regions innervated by those neurons.	Crush injury of one finger causes pain in adjacent fingers also (cervical and thoracic segments).	Toothache in upper jaw may spread to cause faceache and headache (trigeminal).
Muscular	Noxious stimulus causes reflex spasm of muscles innervated by involved segment; persistent spasm causes pain and tenderness.	Pain, tenderness and spasm of loin muscles in renal disease (thoracolumbar segments).	Occipital headache in upper cervical arthritis (C2-3).
Neurogenic	Disorders of neural paths and centres subserving pain sensation (i.e. nerve, posterior root and ganglion, posterior horn, spino-thalamic tract, thalamus; and homologous cranial nerve structures and connexions).	Neuritis, neuralgia, tabetic lightning pains, thalamic syndrome.	Occipital, supraorbital, etc., neuralgia.
Psychogenic	Pain exists only in sensorium (i.e. is 'suprasegmental').	'Cardiac' pain in effort syndrome.	Some kinds of hysterical headache.

TABLE II.—Pain mechanisms and pathways.

safeguard but may be in themselves profoundly upsetting to the organism as a whole'. This is perhaps still the nearest approach we have to an explanation of the emotional origin of vasomotor headache.

The types of headache just described are sometimes called *physiogenic* in contrast to the strictly *psychogenic* headache, in which the pain exists only in the sensorium and has no physical basis at the periphery. This sort of headache is far less common than is often supposed, even in hysteria.

Indeed, Weiss and English (1949) go so far as to say that 'in the last analysis, no headache is imaginary: emotions are quite capable of producing true headache, by their repercussions in the muscles or vessels from which the painful sensations arise'. Clinical experience suggests that truly psychogenic headache often co-exists with physiogenic, emphasizing and exaggerating it —constituting, one might almost say, the familiar 'overlay'.

PAIN MECHANISMS IN HEADACHE

We have now considered briefly the mechanisms by which pain in headache may be produced: these are summarized in Table II. It must be clear that by far the most important sites of origin of the pain are the arteries and the muscles; the latter must especially be emphasized, not only for their importance as prime causes of headaches, but for their ubiquitous presence as causes of intensification, spread and prolongation of pain by reflex spasm. A great many headaches from all causes have an important muscular component which may obscure the real origin. Moreover, even when the underlying primary headache is resistant to treatment, a useful degree of symptomatic relief may be obtained by treating the muscular component by relatively simple physical measures.

It will be understood that pain may be felt in situations other than its site of origin, or may appear to spread peripherally from that site, for several reasons: to wit, segmental reference, central spread, and reflex muscle spasm. The neurology of the head is exceedingly complex, and the interplay of these mechanisms is all too often bewildering as well as fascinating in its infinite variety.

HEADACHE DUE TO DISORDERS OF EXTRACRANIAL STRUCTURES

It would take too long to describe in detail the parts played by the eyes, orbital contents, nose, sinuses, pharynx, jaws, teeth, ears, skull, cervical spine, and soft tissues of the head and neck in the etiology of headache, but a few words may be said to amplify the general principles already discussed.

The sensory innervation of the eyes and orbits is by the trigeminal nerves, and pain arising in them is either felt locally or spread or referred in the trigeminal area, especially in the territory of the first division. Muscular spasm and pain are prominent features of ocular disorders, the affected muscles being the obvious ones (the frowning muscles—orbicularis oculis, procerus, frontalis—and the extrinsic and intrinsic ocular muscles), and the less obvious nuchal muscles. The last are involved because the eyes are closely linked with the complex neurological mechanisms for the maintenance of posture, and the extrinsic ocular muscles have close connexions with the neck muscles via the posterior longitudinal bundle. The whole interesting topic of the relation of eyestrain and ocular disease to headache is admirably set forth by Duke-Elder (1949).

The nose and sinuses also lie for the most part in the trigeminal area,

and pain arising therein is usually referred to the front half of the head, although disease of the sphenoid and posterior ethmoid sinuses may cause vertical, occipital and nuchal pain. Sinus pain tends to be remarkably constant in its time-relationships, recurring and passing off punctually the same time every day in a given patient. It may be said, in passing, that sinusitis is greatly overrated as a cause of headache. In contrast, dental disease is apt to be underrated: malocclusion (Costen, 1936) and many other disorders may be responsible for puzzling temporal headache, probably from spasm of the temporalis muscle.

The sensory innervation of the ears is complex, involving the Vth, VIIth, IXth and Xth cranial nerves, so that the possible area of pain reference is wide; nevertheless, pain arising in the ear is most often felt simply as earache, with or without headache from spread or pain or muscle spasm. Mastoid pain may arise from local disease such as mastoiditis, from a lesion in the cerebello-pontine angle (e.g. an acoustic neuroma) or posterior fossa, and also from spasm of the upper part of the sternomastoid muscle, most often caused by adjacent lymphadenitis.

Disorders of the cervical spine and neck musculature are common causes of headache, especially occipital and nuchal; the pain may spread forward to the vertex, temples and forehead, or may extend down the back or out to the shoulder.

CONCLUSION

I have described briefly the anatomical and physiological basis of headache, the immediate means by which pain is caused and perceived, so far as they are understood. This may usefully and accurately be called the *proximate cause* of headache; it is only part of the story, for there is always an *ultimate cause* as well. For instance, the proximate cause of a 'hangover' headache is cranial arterial pulsation, the ultimate cause over-indulgence the previous night; the proximate cause of headache in a case of intracranial tumour is traction upon pain-sensitive structures, the ultimate cause the growth itself; the proximate cause of a muscular tension headache is persistently increased muscle tone, the ultimate cause emotional tension. And so on. The ultimate cause must always be the diagnostic goal, for only when it is identified and put to rights is it permissible to speak of cure. A knowledge of proximate causes, however, and the part they play helps materially in the search for ultimate causes, provides a rationale for symptomatic treatment when the ultimate cause is inaccessible to diagnosis or refractory to treatment, and renders the whole subject more coherent and comprehensible.

The link between ultimate and proximate causes in the realm of psychosomatic disorder (which embraces the vast majority of headaches) is obscure, despite researches and conjectures by an army of workers on the relation of stress to disease (Wolff, 1953). We know that a certain person has periodic vasomotor headaches of a type we call migrainous, and we therefore say that he has a 'migrainous diathesis': knowing this, we can forecast that if he is subjected to certain strains and stresses he will have more frequent and

more severe headaches. But why does he have headache at all, when in similar circumstances another person might have dyspepsia, another neurodermatitis, and another hypertension? We can give no better reply to this question than Kessel (1930) did twenty-five years ago: that in a given individual a definite reaction picture develops in response to a given emotion. But this is merely talking in a circle.

There is much therefore to be learned about headache; yet if the light shed by recent clinical and experimental studies has not dispersed the darkness, it has at least enabled us to discern a coherent pattern in the scheme of things which we cannot afford to ignore, for the reasons given by the late Professor Ryle in the quotation at the beginning of this article.

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THE VALUE OF ELECTRO-CONVULSIVE THERAPY IN THE NEUROSES

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ELECTRO-CONVULSIVE therapy (E.C.T.) is the most extensively used method today in the treatment of mental disorders, and it has application over a wide range of conditions. Although it is primarily used in the affective psychoses, it is also often employed in the treatment of the neuroses, and, in general practice, conditions such as the milder melancholias and schizoid personalities may be conveniently grouped with the true psychoneuroses (e.g. anxiety states, hysterias, obsessive-compulsive conditions). These form a high proportion of the mental disorders seen and treated outside a mental hospital, and it is the purpose of this article to determine the long-term effect of E.C.T. in these conditions, and to evaluate some factors of prognostic importance.

SCOPE OF INVESTIGATION

The material was taken from the neurosis unit in a general hospital, where both inpatients and outpatients are treated. One hundred unselected patients, who had been treated with E.C.T. by the same investigator, were written to after two to four years had elapsed since treatment. They were asked to re-attend for interview, but those who could not attend were requested to return a questionnaire which asked whether the patient's nerves were now well, if there had been any relapses since treatment, if the patient was working, whether their own doctor was still being attended for nerves; in addition, there was a space for further remarks. Eventually, 77 replies were received, and, of these, 28 attended for personal interview.

Of the total, 34 (44.2 per cent.) were males and 43 (55.8 per cent.) were females. In general, the ages ranged from twenty to sixty years, only three being below twenty years (16, 17 and 18 years) and two over sixty years (both 61 years). Nineteen (24.7 per cent.) were treated as outpatients and 58 (75.3 per cent.) as inpatients, and an average of just over three years had elapsed between treatment and subsequent reassessment.

RESULTS

Fifty-seven, 74.1 per cent. of the total, were found to have remained quite fit ('recovered' group) and the remaining twenty (26 per cent.), who still had nervous symptoms, were therefore classed as 'failures' from the treatment point of view. It should be noted, however, that 13 (65 per cent.) of these 'failures' were working.

Immediately following treatment, the following effects had been noted:—

In the 'recovered' group,

32 (56.1 per cent.) were discharged as 'recovered'
14 (24.6 per cent.) were discharged as 'improved'
11 (19.3 per cent.) showed no immediate change.

In the 'failure' group,

Five (25 per cent.) were discharged as 'recovered'
Six (30 per cent.) were discharged as 'improved'
Nine (45 per cent.) showed no immediate change.

Fifty (65 per cent.) of the total no longer attended their own doctor, and of the remaining 27 who did, many only continued a sedative or placebo habit. Nineteen (95 per cent.) of the 'failure' group, compared with 40 (70 per cent.) of the 'recovered' group, were treated as inpatients.

The 20 'failures' (26 per cent.) were then compared with the 57 'recoveries' (74 per cent.) from various standpoints, and the results are summarized in table I.

	'Recoveries'	'Failures'
Evidence of previous mental breakdown or familial mental instability	49.4%	60%
Duration of symptoms:—		
Less than 3 months	7.8%	5%
Between 3 and 12 months	32.5%	30%
Over 12 months	59.7%	65%
Diagnoses:—		
Anxiety states	39%	45%
Predominantly depressive states	23.4%	15%
Schizoids	15.6%	15%
Hysterical conditions	11.7%	10%
Psychopaths	3.9%	10%
Obsessional neuroses	2.6%	5%
Miscellaneous	3.9%	
Average number of E.C.T.s per patient	4.4	4.05

TABLE I.—Comparison of findings in patients who showed a lasting response to electro-convulsive therapy and in those who did not.

DISCUSSION

Before drawing any conclusions from these figures, there are other factors to be borne in mind. Many neurotics may be improved by any form of enthusiastic medical approach, particularly if it involves admission to hospital. The fact that 95 per cent. of the 'failures', compared with 70 per cent. of the 'recoveries', were treated as inpatients, however, suggests that the hospital regime alone did not contribute materially to recovery. From the point of view of the direct effect of treatment, it will be seen that 80 per cent. of the 'recoveries' showed an immediate response, as also did 55 per cent. of the 'failures'. Thus, over half of the 'failures' showed a transitory

improvement, which might have engendered undue optimism for the treatment had they not been assessed after an appreciable interval. On the other hand, 20 per cent. of the 'recoveries' showed no immediate response, so their subsequent improvement must have been due either to a delayed response to treatment (an effect which is well known) or, in some cases, to the influence of other factors. Sixty per cent. of the 'failures' showed evidence of constitutional instability, but this was also appreciable (nearly 50 per cent.) in those who remained well after approximately three years. When the duration of symptoms is examined, there is no material difference between the two groups, and it is significant that even in the recovered groups nearly 60 per cent. had had symptoms previously lasting over twelve months.

Although this does not fully support the opinions of several authorities upon the adverse effects of constitutional factors, and the long duration of symptoms before treatment, quoted by Monro and Conitzer (1950), it will be observed that these factors were present in a high proportion of the original total group and hence may appear to be excessively represented in the 'recovered' group.

In considering the effects in the different diagnoses, the important question is raised as to whether many of them were really primary emotional disorders. Against this, apart from their presenting symptomatology, is the predominance of the long duration of symptoms, which is unusual in affective syndromes. In discussing the effect of E.C.T. on the depressive states Karagulla (1950) claimed that approximately 30 per cent. had to be readmitted within two to five years of being discharged 'recovered' or 'improved' after E.C.T., and suggested that this was not substantially different from that of a control group who did not have E.C.T. Although her statistical inferences were subsequently criticized by Slater (1951), it is probable that a proportion of our 'recoveries' would have occurred without treatment, albeit more slowly. It is significant, however, that several of our patients spontaneously remarked subsequently that the treatment marked 'the turning point' or that they had 'never felt better than in the years following treatment'.

It will be seen that the anxiety states, schizoids and hysterics are represented by approximately equal percentages in our two groups, and it may be assumed that in the 'recovered' group the depressive component was more marked. As Sargant (1951) states: 'I have never seen good results from E.C.T. in anxiety states, obsessional neurosis or hysteria, unless there was a depressive component, and, even then, results are not comparable to those achieved in the retarded depressions'. Our predominantly depressed states, although representing 23 per cent. of the 'recoveries', also comprised 15 per cent. of the 'failures', but, as our 'failures' were assessed after a prolonged period, it is likely that this formed a high proportion of our 55 per cent. 'failures' who showed a good immediate response, and who subsequently

relapsed. Our psychopathic and obsessional groups showed the greatest resistance to treatment.

CONCLUSIONS

In general, there appears to be a place for E.C.T. in the treatment of the neuroses, and it seems to have a lasting effect upon a proportion of cases. It shows little specificity upon the various diagnoses, although its effect is probably mainly upon the depressive components. In practice, however, it promotes rapid alleviation and sustained improvement in a variety of non-psychotic mental disorders. Psychopathic and obsessional personalities have the poorest prognosis, but the long duration of symptoms before treatment, or the presence of marked constitutional factors, does not necessarily preclude a lasting response.

SUMMARY

The results of a follow-up survey of 77 psychoneurotic patients two to four years after treatment by electro-convulsive therapy at the neurosis centre of a general hospital are discussed, and the sustained effect and prognostic implications are assessed.

Approximately 70 per cent. of the patients are shown to have remained well; 60 per cent. of these had previously had mental symptoms of more than twelve months' duration.

Twenty per cent. of the recovered patients showed a delayed response and, as 95 per cent. of the 'failure' group were treated as inpatients, factors other than the effect of E.C.T. do not appear to have influenced the results.

Psychopathic and obsessional conditions showed the greatest resistance to treatment, but otherwise there was little difference in the effect upon the different diagnoses.

I wish to thank Dr. M. Jeffrey, consultant psychiatrist to the City General Hospital, Sheffield, for his help and facilities in the preparation of this article.

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THE OBSTETRIC EMERGENCY SERVICE

'THE FLYING SQUAD'

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THE coming-of-age of the Newcastle 'flying squad', which answered its first call on October 15, 1935, provides an opportunity for reviewing the development of the obstetric emergency service and its contributions to obstetrics. At a reception, given by the board of governors of the United Newcastle upon Tyne hospitals on February 21, it was reported that the Newcastle flying squad has responded to no less than 1,377 urgent calls. From its inception the number of calls annually increased steadily until 1939, when there were 48. There was then a slight decrease during the war years, but during the last ten years there has been a rapid increase until, in 1955, a peak of 146 calls was reached. At the coming-of-age celebrations tribute was paid to the pioneer work of Emeritus-Professor Farquhar Murray who was largely responsible for the inauguration of the flying squad.

ORIGIN AND DEVELOPMENT

It was realized in 1935 that, whilst some fatalities arose from failure to refer complicated cases to hospital, a certain number of women lost their lives as the result of their transportation. This was especially true of patients with the third-stage complications of hæmorrhage, retained placenta and shock, and it was to this group that the Service was primarily directed.

'Flying squads' are now based on no less than 172 maternity hospitals or units in England and Wales. During the last three months reviewed by the Ministry of Health (April 1 to June 30, 1956) these squads were called on 713 occasions. This implies over 2,800 calls per annum, or, expressed in another way, to 10 of every thousand domiciliary deliveries. Although third-stage complications continue to comprise some 75 to 80 per cent. of the calls, it is pleasing to note that other important uses of the service are steadily unfolding. Abortion, antepartum hæmorrhage, eclampsia, prolonged labour, undiagnosed malpresentations, multiple pregnancies, prolapse of the cord and acute inversion of the uterus are recent examples. Whilst full use of the service is to be encouraged, few obstetricians will deny that more careful selection of patients for domiciliary delivery would effect a material reduction in the strain on the personnel of the squads. Twins, grandmultiparæ, and women with a previous history of third-stage complications should not be

booked for home confinement, for these cases make a considerable contribution to the avoidable causes of maternal death.

PERSONNEL

It is felt that the practitioner and his patient are entitled to the services of an experienced obstetrician, and this has always been the practice in Newcastle. In general it is being adopted by other squads throughout the country. By the same token we expect the practitioner to be present and to remain throughout the emergency. More recently a consultant anæsthetist has been included, and his assistance has proved invaluable. Originally the District Sister was a member of the team, but since the virtual disappearance of the 'Extern Maternity', one or other of the senior sisters in the antenatal department has been responsible for the maintenance of the equipment and invariably accompanies the squad. Her intimate knowledge of the equipment and wide experience in converting the most unpromising environment into an adequate labour room are of great value to the service.

TRANSPORT AND EQUIPMENT

Owing to the considerable distances to be covered (up to 60 miles) by the Newcastle squad, it has always proved more expeditious for the consultants to collect the Sister and the equipment at the hospital. To avoid possible delay, the anæsthetist travels in his own car. This arrangement works well, as all the consultants live within a short distance of the hospital, and it is extremely rare for the patient to be moved to hospital. The equipment is comprehensive and quite adequate to carry out all treatment—even Cæsarean section, but this has only been performed in exceptionally urgent circumstances where the squad was called to a small remote maternity unit. A similar plan has been adopted by about half of the squads throughout the country, but many other types of transport prove more convenient in certain areas, as, for instance, a hospital car, staff car, an ambulance, or a taxi. Squads operating in very restricted areas advocate simple resuscitation and rapid transfer to hospital by ambulance, but we have never regarded this as the proper role for such a service.

ORGANIZATION

In-coming telephone calls are switched direct to the labour room, where a senior sister is always available. The words 'flying squad' secure priority. Sister then informs the antenatal Sister on duty and calls the obstetrician and the anæsthetist. Great care is taken to record accurately the name and full address of the patient, the nature of the emergency, the Rh factor, and the blood group of the patient. The caller is further requested to station at an agreed point near the house a guide, equipped during darkness with a white towel or a large handkerchief for identification. This internal organization is vital to speedy service, and every effort should be made to perfect it by the cooperation of telephone operator, porter, resident doctors and

Sisters. Direct line from exchange to labour room has been suggested. The Winchester group has adopted a system of squared maps with reference numbers by which the practitioner can arrange the precise point for the guide to meet the squad.

SUBSIDIARY EMERGENCY EQUIPMENT

Although the country is reasonably well served by obstetric emergency services, long distances, resulting in inevitable delays, have to be covered in some regions. The number of squads might be increased, but difficulties of competent staffing must be remembered. Consequently the alternative suggestion of emergency equipment decentralized to doctors, district midwives, cottage hospitals or maternity homes has been made—and actually implemented in the Winchester group. This will provide for transfusion while the 'flying squad' is en route. To distribute Group O Rh-negative blood with such equipment would be wasteful, and the view of our blood transfusion service is that plasma substitutes predispose to dangerous afibrinogenæmia. We have therefore been advised to revert to 'small pool' plasma. Ergometrine, 0.5 mg., should be given intravenously, and methylamphetamine may be administered in some cases. The shocked patient should be kept warm but not overheated, and given only minimal sips of fluid in view of the impending anæsthesia. On no account should manual removal of the placenta be attempted until shock has been combated—and the grave danger of transporting a patient to hospital with the placenta *in utero*, even in the absence of bleeding, must be fully appreciated.

THE IMPORTANCE OF THE SERVICE

With the tremendous reduction in puerperal sepsis, the commonest causes of maternal mortality and morbidity are the 'toxæmias' and the 'hæmorrhages'. Improved methods and routine of antenatal care with more careful selection of cases for hospital can still effect further reductions. Early diagnosis and treatment of anæmia, the early detection of pre-eclampsia and hypertension, fuller investigation of the 'high head' in relation to placenta prævia before bleeding, immediate hospitalization (without internal examination) of every case of bleeding, however slight—all these will make their contribution. So long as domiciliary delivery continues, however, there will be need for an efficient 'flying squad' service. As the midwife alone attends many of these patients, she must be permitted to summon the service herself in extreme emergency when she is unable to obtain immediate help from the patient's practitioner.

In order that full advantage may be taken of the service, executive councils and medical officers of health should circulate to practitioners and domiciliary midwives, at regular intervals, information on the location and the method of summoning of 'flying squads' in their areas.

PROBLEMS IN THE HOME NURSING AND CARE OF ELDERLY PEOPLE TODAY

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Dr. Kitching's article in the February issue of *The Practitioner* (p. 234) brings out afresh the increasing problem of elderly people. He talks of the 'disgraceful neglect of the aged sick' and the solution he puts forward is for a new group of women to attend them, who would be part-time 'district assistant nurses'. The leading article in the same journal (p. 143) comments that it is becoming increasingly difficult to be ill at home simply because there is no-one to nurse the patient in his/her own home. This statement may be intended to mean that there are nowadays few relatives at home, or that there are insufficient district nurses.

DISTRICT NURSES

District nurses are of course employed by every local health authority in Great Britain; in fact the number employed is greater than ever before, and the Report of the Ministry of Health (Part I), states that at December 31, 1955, in England and Wales, 9,884 were so employed, compared with 9,642 in 1954. The majority of the nurses are State registered, both Queen's and non-Queen's district nurses, but some (probably 10 per cent. of the total) are State-enrolled assistant nurses. They nurse patients of all ages, including a large number of the elderly sick patients who are under the care of a doctor and are in need of special nursing treatment or of general care, often visiting those who are very ill once or twice daily.

The Ministry of Health Report (Part I) for 1955 also states that over 50 per cent. of the district nurses' visits were paid to people over 65 years of age. Such visits were to give injections and for dressings, general care, rehabilitation and supervision of patients' physical and mental well-being and whatever attention is ordered or needed during visits of an hour or less which district nurses give. Each district nurse probably makes 10 to 15 visits daily, and it is unlikely that the 9000 nurses could do more than they are now doing.

It seems that in areas where recruitment is good there is no shortage of district nurses and all calls which come from the general practitioner, the hospital or the health department can be met by the nurse. In well-served areas, where there is also an adequate supply of home helps as well as help from members of voluntary organizations—British Red Cross Society, St. John Ambulance Brigade, Women's Voluntary Services, National Old

People's Welfare Committees—for providing nursing aids, invalid meals, night sitters-up, laundry services, no such neglect of elderly patients appears to exist. In urban areas with adequate services, there is usually one district nurse undertaking general nursing duties to every 5000 population, and in well-served rural areas, where the district nurse undertakes general nursing duties, and the small amount of domiciliary midwifery—say 14 to 20 cases per annum—there is one district nurse-midwife to every 2000 to 3000 population. It would seem that all patients living in these areas should be adequately nursed. There are, however, badly served areas which have too few nurses appointed, and if sufficient State-registered or State-enrolled assistant nurses are not provided, or allowed for in the agreed establishment, then it is surely the responsibility of the local health authorities to agree to adequate establishments and by all possible means to endeavour to obtain staff.

'DISTRICT ASSISTANT NURSES'

Dr. Kitching, however, appeals for a body of 'district assistant nurses' with duties which are not at present possible, and some which seem inappropriate, for district nurses to undertake. For elderly patients, he wants women who will sleep in the patient's home in emergencies, or sit up all night, or attend at a certain time each day so that patients can be washed and dressed punctually. These women would undertake those services and kindnesses which would be of great comfort and of curative value to patients, and when required to do so, they should be able to perform last offices. He suggests that such helpers would need very little training.

All district nurses will share Dr. Kitching's concern to provide such a useful addition to the services already available, which would undoubtedly be of great help to patients they are attending, and to many others who are not referred to them by doctors because there is no actual nursing treatment required. Such service would be a boon to general practitioners and would enable them to keep their patients in their own homes. It would also allow many individuals the blessing of remaining at home which the large majority long for, even in terminal illness.

It is likely that it would cost the State less to have a patient nursed in his/her own home, attended by the visiting district nurse, with this additional helper, part- or even full-time, than it would cost to maintain him or her in hospital at a cost of £12 to £15 a week.

But is there such a new band of women available to become 'district assistant nurses' working either full- or part-time? Conscription of women to undertake nursing is beyond serious consideration for work, particularly among the elderly, which demands a degree of compassion and a sincere desire to care for others. It seems to me extremely doubtful that such personnel can be found, as most women are already gainfully employed in full- or part-time jobs in other fields such as in factories, shops, and offices, as

well as in part-time nursing. It would seem that such womanpower does not exist, and the only solutions seem to be to widen the duties of home helps and to use more extensively the services of the nursing aids of the St. John Ambulance Brigade and of the British Red Cross Society.

ASSISTANTS TO DISTRICT NURSES

Home helps undertake all types of domestic work and do not normally undertake any nursing or the duties Dr. Kitching pleads for, such as last offices, sleeping in the house and other small kindnesses which a near relative would do. There would seem no reason, however, if they are the right type of individuals, why the duties of home helps should not be widened, especially if they worked as assistants to district nurses, who could teach them such duties as last offices. An increase in their numbers to help district nurses more than they do at present may be necessary. (The Ministry of Health Report (Part I) for 1955 states that 153,439 old people received services from home helps in 1955, compared with 134,571 old people in 1954.)

Voluntary nursing aids of the Red Cross and St. John organizations do give considerable help to district nurses in some areas, chiefly on Sundays and in their own spare time. If their use were encouraged, it is likely that they could be extensively used for the various services which Dr. Kitching mentions by actually assisting district nurses in simple nursing duties, and undertaking last offices for which they have had training. Although members of voluntary organizations, they are allowed to accept financial help in regard to meals and other expenses, and, for example, can receive 10*s.* 6*d.* a night when sitting-up with a patient. If not wearing uniform, they are permitted to accept an appropriate salary as helpers, which may be similar to the recognized scales for home helps.

From every angle, it seems desirable that elderly people should, so far as possible, be allowed to remain at home when they become sick or enfeebled, but there will still be a proportion of patients for whom a hospital bed is the only humanitarian solution. District nurses know of many such patients for whom no beds can be found and they do their best to attend them twice, and occasionally three times a day, but they give harrowing accounts of tragic cases they have nursed: aged and bedsore, gangrenous diabetics, blind persons, hemiplegics who fall out of bed, neglected recluses in dirty homes, and, most sad of all, lonely ill people whose relatives do not visit them.

Recently a Bill was introduced in Parliament by Mr. McLeavy, the Member for Bradford East, which seeks to coordinate the voluntary and public services for the welfare of old people. It will empower local authorities to make schemes to provide old people with meals, recreational and other services. At present they are only able to make grants to voluntary organizations in certain areas and the scope of some voluntary bodies is very limited.

In the House of Lords recently, Lord Amulree called attention to the case of old people, of whom a substantial minority are on the border between health and sickness, neither fit enough to look after themselves, nor yet sick enough to need hospital care. In the ensuing discussion, the Earl of Home thought that the root of the trouble was the lack of personnel to look after these old people in their own homes. He asked for better cooperation between hospital and welfare authorities and said that no Government or Act of Parliament could compel cooperation but, if common sense were applied, great improvements could be made. Lord Cottesloe said in the same debate that what was needed was not such a tidy theoretical solution, but a real understanding and knowledge of the problems and needs of individual old people.

District nurses realize that often the chief cause of unhappiness in the elderly is loneliness, and the feeling that their usefulness has gone and no-one wants their help. Relatives, friends or welfare schemes could do a great deal more to overcome this by providing some useful occupations which they could manage to undertake.

The wide concern expressed by politicians, doctors and district nurses shows that this neglect of old people is a very real problem in certain parts of the country and is likely to increase now that people live longer. It is sad to think that the wonders of medical science in prolonging life by ten to fifteen years may not always prove to be a boon.

FAMILY RESPONSIBILITY

It is saddest of all to think that the family's responsibility to care for the weaker members, the grandparents, the lonely aunt and even the parents, has almost disappeared. Some of our oriental non-Christian peoples put us to shame over this. Can it be that the National Health Service and all the provisions made by the Welfare State are largely responsible for bringing about this state of affairs? It seems that daughters and young wives would rather go out to work and earn, whether or not they really need the money, than stay in the home and undertake the much harder task of looking after those who need their tender care: their young children and their old people. Could any publicity campaign or religious revival ever recover this sense of family responsibility? If it could, it would relieve many problems of physical and especially of mental suffering, because all the nursing and care given by nurses and their auxiliary helpers to elderly people in their own homes, can never really give them the comfort and security that come from knowing that they are wanted and cherished by their own people.

GENERAL PRACTITIONERS' FORUM

PRIMARY TUBERCULOSIS OF THE INTESTINE

By M. H. FRIDJOHN, M.D.
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PRIMARY ileo-cæcal tuberculosis in adults is a very rare condition. Crohn and Jarvis (1940) found eight cases in 4,800 necropsies at Mount Sinai Hospital between 1926 and 1938, whilst Wolfson (1938) met only three cases in 9,100 necropsies between 1925 and 1931. Bockus, Tumen and Kornbloom (1940), after an extensive review of the literature, reported two cases. Horn, Dockerty and Pemberton (1950), in a review of ileo-cæcal tuberculosis, emphasized the difficulty in distinguishing the condition from non-specific regional tuberculosis, whilst Butler (1953) is of the opinion that a large number of cases of so-called ileo-cæcal tuberculosis were probably Crohn's disease, as evidenced by a series of cases observed between 1937-52. Ukil (1942) analysed 1000 cases of intestinal tuberculosis and found 9 per cent. to be primary in origin.

In ileo-cæcal tuberculosis the gastro-intestinal symptoms commonly consist of abdominal pain, nausea, vomiting, anorexia, discomfort after meals, diarrhœa or constipation. Sometimes few of these symptoms may be present. In addition there may be loss of weight, fever, weakness, night sweats and psychotic disturbances. As these symptoms may simulate so many other disorders extensive investigation may be necessary to establish a diagnosis.

CASE REPORT

Mrs. S., aged 56 years, was seen by one of us (M.H.F.) on Dec. 12, 1954, when she complained of lassitude and loss of weight in the preceding four months. She had become extremely depressed. She stated that she had lost her appetite and on occasions suffered from nausea but did not vomit. She had never suffered from abdominal pain. She was constipated and the bowels only acted properly when she took purgatives. There was no history of diarrhœa or of the presence of blood or slime. There were no urinary symptoms. She had no cough. She had lived in India for about twenty years and had only returned to this country a year ago. She had never contracted any tropical disease. Apart from hysterectomy for a fibroid uterus in 1938 her previous history was uneventful.

On examination she appeared a frail middle-aged woman whose height was 5 feet 7 inches (170 cm.) and weight was 8 stone 2 pounds (52 kg.). She stated that she had weighed over 11 stone (70 kg.) in the previous September. She was afebrile and the pulse was 86 per minute. The conjunctivæ were pale. She was edentulous and the tongue was clean. The thyroid gland did not appear enlarged. There was no evidence of lymphadenopathy, and there was no œdema of the lower extremities. No abnormality was detected in the respiratory or cardiovascular systems. The blood pressure was 140/90 mm. Hg. Palpation of the abdomen and pelvic examination revealed no abnormality apart from the absence of the uterus.

A provisional diagnosis of carcinoma of the bowel or of the stomach was considered and arrangements were made for her to be investigated in hospital.

Ten days later she was seen again at her home. Her husband stated that for about a week she had been running a temperature of 100° F. (37.8° C.) at night, the morning temperature being normal. The depression was now more severe. She was still constipated. The clinical findings were similar to those found originally.

Two days later she was removed to hospital where the following investigations were performed:—

Blood count: R.B.C. 4,200,000 per c.mm. Hæmoglobin 82 per cent. C.I. 0.97. W.B.C. 6000 per c.mm. Polymorphs 65 per cent. Lymphocytes 30 per cent. Monocytes 4 per cent. Eosinophils 1 per cent.

Erythrocyte sedimentation rate: 20 mm. in first hour.

X-ray of chest: No abnormality detected.

Barium enema: Small diverticulæ of the colon.

Barium meal: Negative.

Intravenous pyelogram: Negative.

Urine: A few pus cells. No red cells. Very faint trace of albumin. No tubercle bacilli found on culture.

Fæces: Shigella sonnei, shigæ and *flexneri*—negative.

Blood: Culture: No growth after prolonged incubation. Total protein 5.5 g. per cent.: albumin 2.7 g. per cent., globulin 2.8 g. per cent. Electrophoresis confirmed diminished albumin and showed marked emphasis of alpha globulins and a moderate increase in gamma globulins—suggestive of tissue necrosis connected with neoplasm or abscess. *B. paratyphosus B.* (H) positive to a titre 1/20. No agglutination with *B. typhosus* (H and O), *B. paratyphosus B.* (O). Wassermann and Kahn reactions negative. Complement fixation tests for influenza A and B, psittacosis and Q fever negative at 1/4. *Strep.* M.G. agglutination negative at 1/20.

FIG. 1.—Ileo-cæcal junction showing tubercles.

While in hospital the temperature became remittent, the maximum being 103° F. (39.4° C.) in the evening. Penicillin, 1 mega unit twice daily for five days, had no effect on the temperature, whilst 1 gramme of streptomycin three times daily for one week did reduce the evening temperature to 100° F. (37.8° C.). She was seen by a consulting surgeon who confirmed the diagnosis of carcinoma and considered laparotomy was unjustified in view of her poor condition. After a fortnight she weighed only 6 stone 7 pounds (41 kg.). She had become progressively weaker and her hæmoglobin was 40 per cent. Acute depressive melancholia was well marked. A week before her death she developed diarrhœa and incontinence of fæces. Her condition deteriorated rapidly and she died four weeks after admission.

Post-mortem examination revealed the presence of numerous yellowish nodules in the distal two feet (60 cm.) of the small intestine. The nodules were in clusters and associated with localized thickening of the gut wall. No ulceration of the mucosa was present. The lesions were suggestive of either Crohn's disease, tuberculosis or carcinomatosis (fig 1). Sections of these nodules revealed the presence of characteristic giant cells, and tubercle bacilli were seen in one specimen. No abnormality was found in any other organs.

DISCUSSION

It would appear that this patient must have contracted intestinal tuberculosis from drinking infected milk, probably in India. During the first few months of the illness the disease manifested itself by lassitude, anorexia, nausea, constipation, and loss of weight. Abdominal pain was never present, and diarrhœa only developed a week before death. Acute depression was a well-marked feature of the case. The toxæmia was most severe in view of the limited extent of the lesions found at post-mortem examination.

The diagnosis of carcinoma of the bowel appeared so strong that a barium enema was the first line of investigation, and the question of ileo-cæcal tuberculosis was not considered. A follow-through after a barium meal and an examination of the stools for tubercle bacilli would certainly have established a correct diagnosis. A more careful assessment of the effect of streptomycin in reducing the diurnal range in temperature might have offered a helpful clue.

SUMMARY

A case of primary ileo-cæcal tuberculosis is described, the duration of the illness being short, and accompanied by a profound toxæmia. The importance of a full x-ray investigation together with an examination of the fæces for tubercle bacilli is stressed.

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THE USE OF PHENYLBUTAZONE IN THE TREATMENT OF SUPERFICIAL THROMBOPHLEBITIS

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Acute superficial thrombophlebitis remains a fairly common disorder in general practice. In the past, treatment has entailed bed rest, soaks, antibiotics and local medications, usually effective but seldom bringing prompt relief and often definitely protracted. Following claims by Stein (1954, 1955), in the United States, that phenylbutazone was a more rapid and effective means of treatment, we decided to use it in selected cases in our practice.

METHOD

Recognizing the known contraindications to the use of the drug, we did not give it to any patient in whom there was any fear of cardiac decompensation, or who had a history of peptic ulceration, blood dyscrasia or drug allergy—nor in patients with hypertension or renal or hepatic damage.

No treatment apart from phenylbutazone was given, and all patients were kept ambulant except the two suffering from malignant disease who were, in any case, confined to bed before the onset of phlebitis. We decided to use an average dose—100 mg. thrice daily—and eventually found that in no case was a total dosage of more than 1.5 g. given.

We have now treated fifteen such cases in this way. Varicose veins were the etiological factor in twelve of the fifteen, malignant disease in two, and in the other case the phlebitis occurred spontaneously in clinically normal veins and was presumably idiopathic migratory thrombophlebitis—a finding in agreement with Stein's much larger series. In general practice, of course, we did not see any drug or chemically induced phlebitis due to intravenous therapy.

RESULTS

We found that treatment was remarkably successful and safe (table I). In all but one of the cases pain in the affected limb had disappeared or was considerably lessened within twenty-four hours. In three days all local redness and swelling over the inflamed area had disappeared, and any accompanying systemic upset with fever and malaise had also regressed.

Type of superficial thrombosis	No. of cases	Resolution	
		Complete	Incomplete
In varicose veins	12	12	0
In malignant disease	2	1	1
In idiopathic migratory phlebitis	1	1	0

TABLE I.—Results obtained with phenylbutazone in 15 cases of superficial thrombophlebitis.

Only in one case was recovery temporary, and that was a man who had an inoperable carcinoma of the lung and in whom the phlebitis was soon overshadowed by other disease processes.

The following are three typical case histories:—

Case No. 1.—Mr. F., age 48 years, had recurrent superficial thrombophlebitis. For 23 years he had, every second or third year, to spend up to three weeks in bed on account of thrombophlebitis of one or other leg. In 1953, when in hospital, he was attended by one of us (H.H.A.E.) following a superficial phlebitis of the left leg—the deep veins of the calf became involved and he had a pulmonary infarction. At one stage his employment was threatened as he was off work so constantly.

In January 1956, he again had a superficial thrombophlebitis of the left leg. This time he was given phenylbutazone, 100 mg. thrice daily, and told to stay at work. In three days the inflammation had gone, all redness and tenderness over

the vein had disappeared and the leg was much less swollen. In seven days the leg was completely normal.

Since this episode, on several occasions the patient, an intelligent man, has been aware that a superficial thrombophlebitis was about to recur and taken 100 mg. thrice daily for two days, completely aborting the attack.

Case No. 2.—Mrs. C., age 58 years, had already been in bed for three weeks receiving local applications and the like when we first saw her. She was then put on phenylbutazone. In three days she had started to get up and walk around, all pain, redness and swelling having disappeared.

Case No. 3.—Mr. W., age 72 years, had been in bed for a month because of cachexia associated with inoperable carcinoma of the prostate, when he developed superficial thrombophlebitis of the left leg. After five days on phenylbutazone his leg looked and felt as normal as its fellow, apart from some cord-like thickening where the veins had thrombosed.

COMMENT

We believe that phenylbutazone is a valuable and efficacious drug in the treatment of superficial thrombophlebitis in general practice. As the dosage employed to obtain resolution of the inflammatory process is small, the possibility of side-effects or dangerous toxic reactions is considerably reduced and we have no complications to report.

The rapidity of resolution on this treatment represents a valuable reduction in time spent in bed and in economic loss. The avoidance of bed rest, made possible largely by rapid control of systemic upset and pain must, we believe, reduce considerably the incidence of deep vein thrombosis and the unpleasant complication of pulmonary embolism.

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A TALE OF GIN

By A GENERAL PRACTITIONER

One day last spring I was summoned to attend a patient of another doctor who had gone on holiday, and for whose patients I was 'on call'. The man was fairly moribund, and dying in that state of misery, pain and wretchedness which so often accompanies the terminal stages of malignant disease. I therefore prescribed for him, without hesitation, what I had so often dispensed in my previous sphere as a qualified pharmacist, namely, 'Haustus Euphoriens': morphine and cocaine in a vehicle of honey and gin.

GIN NOT A 'DRUG'

Within a matter of weeks, I was informed, as I expected, that the gin was not a 'drug', but that I had the right of appeal to our local medical com-

mittee. Just before my appeal was due to be heard the July issue of *The Practitioner* came to hand, and, to my joy and pleasure, in an excellent article by Dr. Douglas G. French, of Kidsgrove, there appeared (p. 85) the replica of my prescription. By an extraordinary coincidence that week also, I received a copy of *Clinical Excerpts*, in which my prescription was again identically repeated. Armed with these two publications, confident in the rectitude of my conscientious prescribing, confident in the full support of colleagues who, I expected, would say 'his action was right, we acknowledge the proof he has brought', confident that I would be allowed to pass the two journals round the committee, I was shocked to find that the members of the committee were interested in neither the case nor my principles, and had already decided that I was wrong, whatever sort of justification I put up.

Shocked and angered by this attitude, which was confirmed by their letter saying the medical committee had failed to support me but that I still had the right of appeal to the Minister, or at least to his referees, I appealed, explaining the case, and sending forward the two aforementioned publications.

THE SEQUEL

After some weeks, the following facts emerged. In the absence of the patient's own doctor, I was in the position of 'locum' for him, and hence I could not be charged for the gin. The patient's doctor, now faced with the staggering bill of 8*s.* 1*d.*, checked his records and found that he had been treating this man, amongst others, who had never been on his list, and for whom, and for 30 years, he had never received any payment. Further, this man was to all intents and purposes a phantom for he did not even appear in the records of the executive council.

To save embarrassment all round, it was arranged that I should withdraw my appeal, and that the case should be dropped into the limbo of forgotten things.

THE POINT AT ISSUE

What still worries me, however, is this: I virtually followed out the prescription, or recommendation, of a contributor (of considerable standing) to *The Practitioner*, a periodical which I take to be recognized as an organ of *good* general practice. This recommendation, however, did not receive either confirmation *or* approbation, in the light of present-day National Health Service trends, which of course are those that we as general practitioners must recognize. I know that Dr. C. A. Clarke (*The Practitioner*, 1957, **178**, 38) has subsequently given us a way of getting round this Ministerial ban on the medicinal use of gin. Such subterfuges, however, are scarcely in keeping with professional standards of conduct, and therefore I still feel that a matter of principle is at stake. By what standards are we general practitioners to be guided? Those of the medical journals we read, or those of the bureaucrats of Savile Row and St. Andrew's House?

HOW TO WRITE A MEDICAL BOOK

By M. O'DONNELL, M.B., B.Chir.
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This article is designed neither for the inarticulate physician nor for the frustrated 'littérateur'. It is written to enable junior members of the profession to overcome the most serious difficulty that faces them today—how to earn some money. Personal investigation (Cope's and Vernon's 1955; Littlewood's 1956) has convinced me that one of the simpler methods of tackling this problem is to write a book, and considering them from a purely remunerative angle I have found that medical books fall into four main categories.

CLASSIFICATION

Group 'A'.—The COMMERCIAL Medical Book.

This is for the truly lazy and avaricious author. The sole qualification which places a book in this category is the inclusion of one of the following phrases in the title. (They are starred according to selling power.)

* * * * Sexual behaviour.
* * * Marital technique.
* * Talks for young girls (or boys, or both).
* Diseases of the female.

Group 'B'.—The MEMOIR.

Properly handled this can be a very strong seller. Titles range from 'The world was my practice' to 'Fifty years of fibroids in the Faroes'. To push sales really effectively get a photograph of one of your middle-aged uncles, preferably smoking a pipe, and stick it on the back of the dust jacket labelled 'The Author'.

Group 'C'.—The TEXTBOOK.

If you are in the position to compel students to buy this, it can be the best investment of all.

Group 'D'.—The ARTICLE.

This is mentioned merely for the sake of completeness. It earns nothing save a certain amount of kudos in somewhat rarefied circles. Titles tend to be longwinded: e.g. 'Some further considerations of the morphology of the third metatarsal in the Nicaraguan'.

THE 'FILLING'

Once the group and the title have been chosen, the immediate consideration is the 'filling'.

Group 'A'.—Here the 'filling' is quite simple. One merely paraphrases

the relevant chapters in 'Ten Teachers', Marie Stopes or *The Church Lad's Gazette*.

Group 'B'.—The 'filling' is a little more difficult. It must have what the critics call 'conflict' and what you and I call a good story. Get one of your patients to tell you one. Then pad it out with young probationers falling in love with middle-aged physicians, middle-aged physicians falling in love with young probationers and middle-aged surgeons falling in love with themselves.

The ending is very important. It must be one of two types: (a) Everything turns out all right. (b) Everything turns out all wrong. There must be no compromise between the two.

Group 'C'.—Here the 'filling' is of no importance. The only important thing is the preface and at least half of this must consist of acknowledgments. Prominent among these must be your debt to your wife. (If your home life is unhappy, substitute 'devoted secretary'.)

You must thank your senior colleagues for unsolicited advice which you never followed and I cannot overstress the importance of one long paragraph expressing eternal indebtedness to some obscure professor in Equatorial Africa 'for his inestimable kindness in lending the photograph of the Nigerian knee-cap opposite page 583'. It is essential that this eulogy should be at least three times as long as the paragraph thanking your junior colleagues who have compiled the index, assembled the statistics, collected the cases, annotated the bibliography and who have, in short, written everything in the book except the preface.

CONCLUSION

Charles Churchill (1731-64) wrote in 'The Ghost' (bk. iii, 1, 801):

> 'He for subscribers baits his hook,
> And takes your cash; but where's the book?'

It is suggested that impoverished members of the medical profession show him precisely where it is.

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CURRENT THERAPEUTICS

CXII.—PENICILLIN V

(PHENOXYMETHYLPENICILLIN)

By JOHN MACLEOD, M.B., F.R.C.P.Ed.

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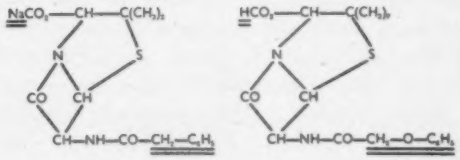
THERE have been three main stages in the evolution of the penicillins for therapeutic purposes. First there were the potassium, sodium and other salts of the organic acids produced by *Penicillium notatum*, of which the most important is benzylpenicillin (penicillin G). Then came the salts of benzylpenicillin with organic bases, such as procaine benzylpenicillin, benzathine penicillin and benethamine penicillin, the main contribution of which was to prolong the action of penicillin. Now penicillin V is available. This is a new form of penicillin which is prepared by adding N-(2-hydroxyethyl)-phenoxyacetamide to the medium in which the mould is growing. As is indicated by its official name, phenoxymethylpenicillin, penicillin V differs from penicillin G in that a phenoxymethyl group replaces the benzyl group:—



It will be seen from the structural formulæ that there is a difference of only one oxygen linkage between the two preparations, and that one is an acid and the other a salt. Benzylpenicillin is stable only in the form of a salt, whereas phenoxymethylpenicillin is stable either as an acid or a salt. It is as the free acid that the latter is at present marketed and its stability in acid media confers on it its unique properties.

Penicillin V was first prepared in the United States by Behrens and his colleagues (1948). The significance of its stability in the pH range below 5 was recognized when it was investigated some five years later in Austria by Brunner (1953) and by Brandl and Margreiter (1954). This property renders penicillin V much more resistant to inactivation by gastric juice than other oral penicillins. These workers also demonstrated that this preparation was readily absorbed from the intestinal tract when given by mouth. Since then it has been used with increasing frequency, and in 1955 it was

claimed that in Sweden some 40 per cent., and in Austria some 30 per cent., of all penicillin prescribed was penicillin V.

There are varying quantitative differences in the action of penicillin V against the organisms used in biological assay and its measurement in units is not practicable. Dosage is therefore determined in milligrams. *By chemical assay 60 mg. of penicillin V is equivalent to 100,000 units of penicillin G.*

ABSORPTION, BLOOD CONCENTRATION AND EXCRETION

Penicillin V is unaltered by its passage through the stomach, whether taken before or after a meal. It is soluble in the alkaline contents of the proximal small intestine and is readily absorbed. The residue is inactivated by penicillinase in the lower bowel and is therefore unlikely to disturb the balance of the intestinal flora. In assessing the blood levels, comparison with penicillin G, rather than with benzathine penicillin, is desirable, as initial claims that the latter antibiotic is better absorbed from the gut and gives higher blood levels than the former have not been substantiated by later workers such as Bayne *et al.* (1953) and Fairbrother and Daber (1954). The Austrian claims that penicillin V produces blood levels considerably higher and more prolonged than those following an equivalent dose of penicillin G have now been confirmed by many other workers, including Wright *et al.* (1955), Martin *et al.* (1955), and Rinsler and Cunliffe (1956). The last of these showed that the levels attained after 120 mg. of penicillin V were about double those following an equivalent dose of penicillin G, and compared favourably with the blood levels following 100,000 units of penicillin G given by intramuscular injection. It has also been established that penicillin V gives much higher and more prolonged blood levels than benzathine penicillin given by mouth (Henry *et al.*, 1957).

Difficulties from malabsorption from the small intestine, such as have occurred with penicillin G in some individuals, have not so far been reported. Penicillin V is rather more slowly absorbed and takes slightly longer to produce its highest blood level than penicillin G, but any disadvantage of this delay is outweighed by the much higher and more prolonged levels which are reached. Detectable blood levels are still present six hours after the administration of 120 mg. of penicillin V, whilst none is detectable at this time after an equivalent dose of penicillin G. In children adequate blood levels may reasonably be expected up to three hours and possibly up to five hours after 120 mg. of penicillin V (Holborrow, Bywaters and Johnson, 1956). These authors also point out that higher blood levels are obtained when this preparation is given half an hour after food than if it is taken one hour before food. Others, such as Jones and Finland (1955), have demonstrated a similar effect of meals on absorption. Very much higher levels can be produced by the concurrent administration of probenecid which inhibits the excretion of penicillin V by the renal tubules. The levels are three to four times greater than those produced by equivalent doses of penicillin G and probenecid (Cox *et al.*, 1957).

Penicillin V is widely diffused throughout the body. It passes into pleural and ascitic fluids but not into the cerebrospinal fluid. It is excreted in the bile and in the urine. About a quarter of the dose given can be recovered from the urine. Whilst this is about twice as much as in the case of penicillin G, and points to the inferior stability of the latter, it also indicates that absorption of penicillin V is by no means complete. This 25 per cent. excretion of the phenoxymethyl derivative compares unfavourably with the 60 per cent. which is excreted in the urine when penicillin is administered by injection.

ANTIBACTERIAL ACTIVITY

For all practical purposes the spectra of penicillins V and G are the same. There are some minor differences: for example staphylococci tend to be more sensitive to penicillin V and some streptococci are more sensitive to penicillin G.

PREPARATIONS, DOSAGE AND COST

Penicillin V is available in tablets containing 60 mg. and in capsules containing 60 mg., 125 mg., or 250 mg. Palatable suspensions are dispensed for administering the antibiotic to children. An average dose for an adult suffering from an infection of moderate severity due to an organism sensitive to penicillin is of the order of 120 mg. four-hourly, the last two doses being administered together before retiring. For children half the adult dose and for infants one-quarter of the adult dose are prescribed. The antibiotic should preferably be given after food in order to take advantage of the higher blood levels that result. If it is desirable to avoid any delay in obtaining an effective blood level an initial injection of 100,000 units of penicillin G is indicated. If very high blood levels are required from oral medication, penicillin V may be given in doses of 240 mg. or more, or combined with probenecid (0.5 g. six-hourly or twelve-hourly).

The current retail price of penicillin V in doses of 120 mg. four-hourly for five days is about twenty shillings. In comparison, 600,000 units of procaine benzylpenicillin once daily for this period would cost about half this price, but other expenses, difficult to compute, are incurred when any preparation is given by injection. The price of penicillin V compares increasingly favourably with penicillin G given intramuscularly in proportion to the number of injections given. It must be remembered, however, that sulphadimidine is still less expensive.

CLINICAL APPLICATIONS

Clinical trials conducted in Europe and America have produced very encouraging results in a wide variety of infections due to penicillin-sensitive organisms. Streptococcal infections (tonsillitis, pharyngitis, bronchopneumonia and erysipelas), pneumococcal infections (lobar pneumonia) staphylococcal infections (carbuncles and osteomyelitis) and spirochætal infections (Vincent's angina) have all been treated successfully. Uniformly good results have been reported from Great Britain in the treatment of

a miscellaneous group of conditions of this type in general practice by Bowerbank (1955), Dove (1955) and Jolles (1956); in hospital practice in the United States by Martin *et al.* (1955) and by Wood *et al.* (1956); and in Europe, both in and out of hospital, by Hausmann and Zischinsky (1953) and by Schindelmaisser (1954). In dental practice, conditions such as apical abscesses and osteitis have been treated successfully by Herrmann (1955).

More detailed studies of the effect of penicillin V in specific conditions are now becoming available. Patients suffering from lobar *pneumonia* or other respiratory infections, including broncho-pneumonia, were treated either with penicillin G by intramuscular injection (1 mega to 1.2 mega units daily), or with penicillin V (60 to 120 mg. four-hourly for at least five days), at St. Stephen's Hospital, London, by Hart and his colleagues (1956). The selection of the method of treatment was made at random, two comparable groups of 12 cases were studied and the clinical response was roughly identical. The patients preferred the oral treatment. The authors suggested that penicillin V would prove to be a practical alternative to parenteral penicillin which should be particularly useful in busy general practice. At the 1956 Symposium on Antibiotics at Washington, McWhorter and his colleagues from Cincinnati found that penicillin V, in doses varying from 375 mg. every four hours to 300 mg. every six hours, was effective in the treatment of patients moderately or severely ill with lobar pneumonia. On the other hand, the efficacy of sulphadimidine in the treatment of this condition must not be forgotten.

Breese and Disney (1956) have treated 110 children in Rochester, N.Y., suffering from *β-hæmolytic streptococcal infections*. The clinical response was excellent and cultures rapidly became negative. They claimed an overall 'cure' of approximately 90 per cent.

Encouraging results have been obtained in acute *gonorrhœal urethritis* by Marmell and Prigot (1956) and by Love and Weir (1956).

Subacute bacterial endocarditis should provide a critical test of the therapeutic efficiency of penicillin V. Results have been claimed which compare favourably with those achieved by the parenteral administration of penicillin G. Quin and his colleagues (1956) treated four patients with subacute bacterial endocarditis. Two of these with a *Streptococcus viridans* infection were treated with 7,200 mg. daily for six weeks and showed a satisfactory clinical and bacteriological response. A third case was due to an unusual organism, *Neisseria sicca*, and was treated successfully with penicillin V orally and streptomycin intramuscularly. In the fourth patient remission could not be maintained but the infection proved to be due to a penicillin-resistant staphylococcus. In one case success has been claimed with two weeks' treatment when penicillin V was supplemented with streptomycin (Martin *et al.*, 1956). At the Symposium on Antibiotics in 1956, Cox and his colleagues reported success in the treatment of 13 out of 14 cases of the disease using 'a high oral dose regime of penicillin V'.

Much further careful study will obviously be necessary before it is possible

to say whether penicillin V given orally will have a place in the treatment of subacute bacterial endocarditis, but the encouraging results already obtained are an indication of its potency in a severe infection.

It has thus been established that penicillin V in doses of 240 mg. four-hourly is effective in patients seriously ill from infections due to penicillin-sensitive organisms, but the use of penicillin V in these circumstances is still at a stage when there must be a most critical appraisal of the results obtained. It will often be necessary to supplement penicillin V with penicillin G by intramuscular injection, at the initiation of treatment in urgent cases, or by local injection, in infections of the joints or of the pleural cavity.

ADVERSE EFFECTS

Penicillin V has been administered for long periods in very large doses to animals and to humans without adverse effects. Glassman and his colleagues (1956) studied tissue sections from animals in these circumstances and found no evidence of any specific damage in organs such as the liver or in the bone marrow. Diarrhœa may be troublesome but is rare and seldom interferes with treatment. It is presumably the result of an alteration in the intestinal flora. Sore tongue and vomiting have been reported but not as more than temporary inconveniences.

Sensitivity phenomena ranging from mild erythema to frank 'serum sickness' occur infrequently. In the report on new and non-official remedies by the American Council on Pharmacy and Chemistry (1956) it is stated that in rare instances penicillin V may cause acute anaphylactic shock, although this is less likely than after the parenteral administration of other penicillin preparations. No details of specific instances are given in this report and I have not come across any account in the literature of such a happening, although severe anaphylactic reactions have been described following the use of other oral penicillins. I have had the opportunity of discussing this problem with many practitioners who have used penicillin V extensively and none has encountered any serious difficulty from sensitivity phenomena. Clearly, however, penicillin V must be used with caution in patients with a history of asthma or allergy.

A history of sensitivity to penicillin G does not necessarily mean that the patient will be sensitive to penicillin V. This absence of cross-sensitivity in many cases appreciably adds to the usefulness of penicillin V in view of the increasingly high incidence of sensitivity to penicillin G. Another advantage of the former is that doctors and nurses do not have to handle the preparation and therefore run little risk of becoming sensitized in the course of their work.

CONCLUSIONS

Penicillin V is the penicillin of choice for oral use.

Penicillin V given by mouth is as effective as penicillin G given intramuscularly in the treatment of pneumococcal and hæmolytic streptococcal infections and may be more effective in the treatment of staphylococcal

infections. In these circumstances it is to be preferred to parenteral penicillin if the patient is reliable, has no difficulty in swallowing and is not vomiting.

A dosage of 120 mg. four-hourly gives blood levels which compare favourably with those produced by 100,000 units of penicillin G intramuscularly and is adequate for adults suffering from infections of moderate severity. It is preferable to give the antibiotic after meals and the last two doses may be administered together on retiring. For severe infections 240 mg. or more four-hourly will be required, and in urgent cases it is desirable to supplement treatment at the outset with penicillin G by intramuscular injection.

Further carefully supervised studies will be required to ascertain the efficacy of penicillin V in the treatment of gonorrhœa and subacute bacterial endocarditis and in the prophylaxis of streptococcal infections.

Penicillin V is very well tolerated and unlikely to cause any harmful effects other than slight diarrhœa or an occasional sensitivity reaction. Patients who are sensitive to penicillin G are not necessarily so to penicillin V, but in these circumstances the latter must be given with caution.

Until more experience of the effects of penicillin V is available it is essential that physicians should continue to be highly critical of its therapeutic efficiency and to be on the alert for any adverse effects.

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EQUIPPING THE SURGERY

IV.—THE OPHTHALMOSCOPE

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'But, soft, what light through yonder window breaks?'
Romeo and Juliet.

WHEN, in 1851, Helmholtz discovered the ophthalmoscope von Graefe cried 'Helmholtz hat uns eine neue Welt erschlossen'. The credit for being the first man to see the living human fundus should perhaps be given to Charles Babbage, an English mathematician who, in 1847, projected a beam of light into the subject's eye from a mirror through a hole in the centre of which he observed the beam reflected from the retina of the subject. This idea, however, was not published until seven years later.

HOW IT WAS DEVELOPED

The principle having been established, improvements and modifications followed rapidly. A concave mirror was used as a reflector increasing the illumination; a case carrying a battery of different-powered lenses was fitted behind the aperture. The *indirect* method was evolved and compact easily handled instruments were designed by various makers. Illumination of the reflecting ophthalmoscope in early days was by oil-lamp, then by naked gas-flame and later the incandescent mantle, followed by the carbon-filament electric bulb. The introduction of small torch-bulbs and dry-batteries led the way for the self-luminous or *electric* ophthalmoscope, the forerunner of the stream-lined instruments we use today in which the current is supplied by a battery in the handle or, through a transformer, from the mains supply. Juler introduced a prototype into England in 1886, but the electric ophthalmoscope only came into general use in this country between the turn of the century and the 1914-18 War, and in continental clinics the non-luminous ophthalmoscope was used in teaching clinics right into the twenties.

HOW IT IS USED

There are two main methods of ophthalmoscopy: the *indirect* method and the *direct* method, each with its own technique and relative advantages.

(a) *Indirect method.*—The apparatus is simple. The source of illumination, a frosted filament-bulb, is placed just above the patient's head. The examiner is seated at arm's length from the patient and holds in front of his eye a concave mirror with a hole in the centre (fig. 1). A beam of light is directed through the patient's pupil: the beam is reflected by the retina and is

brought to a focus by a 13-diopter lens held in the examiner's left hand in front of the patient's eye. The focused image of the retina is a real, inverted image, magnified about five diameters. In order to see the disc the beam must be directed through the patient's pupil in the direction of the centre of the patient's head, the patient looking straight ahead. The eye of the examiner, the convex lens and the pupil of the patient must be in the same horizontal plane. The examiner, by moving his head and the lens in various directions, can examine the region surrounding the disc. The peripheral region is examined by directing the patient to move his eye, not his head, up-and-in, directly up, up-and-out and so on, until the fundus is traversed in every direction.

FIG. 1.—Indirect ophthalmoscopy.

(b) *Direct method.*—The electric or self-luminous ophthalmoscope, as opposed to the older *reflecting* model, is now favoured in using the direct method. The hood of the ophthalmoscope is supported by the examiner's eyebrow and the ophthalmoscope is brought directly in front of the patient's eye and as close as possible, so that the examiner's and patient's eyebrows are almost brushing (fig. 2). The examiner should use his right eye for the patient's right eye and vice versa. When the examiner and patient are both emmetropic the examiner looks through the sight-hole and obtains a clear view of the fundus without an intervening lens. When either patient or observer is ametropic a suitable lens is rotated in front of the sight-hole. The image is erect, is virtual, and the magnification is about 15 diameters.

FIG. 2.—Direct ophthalmoscopy.

A pattern of instrument which is popular is the Lister-Morton self-luminous ophthalmoscope (fig. 3). It is a sturdy instrument

which will withstand a fall and although it is fairly costly (about £20) it will last a life-time. Another deservedly popular model is the 'wide-angle' ophthalmoscope. Other instruments, with trimmings such as slits and filters, are more vulnerable but should not be overlooked in choosing an instrument.

The preliminary examination of the fundus is best carried out by the indirect method for, although the magnification is less, the field in any given direction is wider and it can be used independent of errors of refraction in the patient's eye. The direct method, with its higher magnification, facilitates

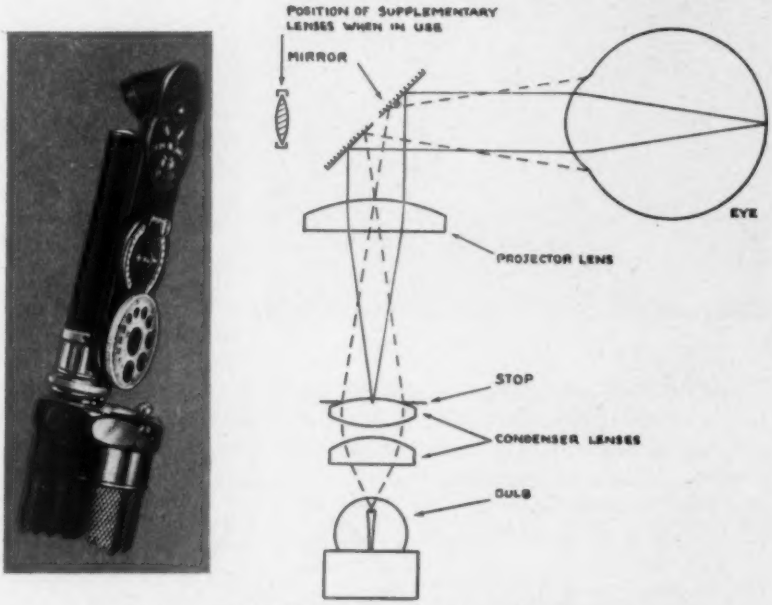

FIG. 3.—The Lister-Morton self-luminous ophthalmoscope.

a minute examination of any detail in the fundus to which attention has been drawn by the indirect method.

MODIFICATIONS OF OPHTHALMOSCOPY

The fundus may be examined by *red-free light*, inserting a green filter in the sight-hole of the ophthalmoscope.

The vessels appear black against the yellowish-green background and the actual nerve-fibres of the retina can be seen. The slit-lamp and corneal-microscope can be adapted to permit of *binocular ophthalmoscopy*. The fundus can be demonstrated to students by the *demonstration ophthalmoscope* (fig. 4) in which branch viewing-tubes are spread out, octopus-like, from the main viewing-tube, so that the demonstrator and as many as eight students can view the fundus simultaneously. Cameras have been designed to *photograph* the fundus and clinical artists have been trained to *paint* fundus pictures.

It cannot, however, be too strongly urged that the ophthalmologist or other clinician who is using an ophthalmoscope should train himself to make a sketch-drawing of every unusual fundus. Even a rough sketch showing the disc and the blood vessels with anomalous features marked in their respective positions is often more valuable than many lines of written description.

FIG. 4.—Demonstration ophthalmoscope.

WHAT TO LOOK FOR

The ophthalmoscope can be used as a torch-beam to illuminate the anterior segment of the eye and, in conjunction with a corneal-loupe, the cornea can be examined minutely. By oblique or by direct illumination the iris and lens can be examined; and the vitreous can be examined directly with appropriate lenses rotated in front of the sight-hole of the direct ophthalmoscope to bring opacities in that medium into focus. The ophthalmoscope can also be used to estimate errors of refraction. The unique and *essential* purpose of ophthalmoscopy, however, is to examine the living fundus or background of the eye (fig. 5). The fundus comprises that part of the retina which can be seen by the ophthalmoscope, with the optic disc, the macula, the blood vessels and anomalies or abnormalities of any or all of these. There is no standard-pattern fundus and its appearance, even in healthy subjects, is so protean that it is only by examining every known normal fundus that variations can accurately be known as pathological.

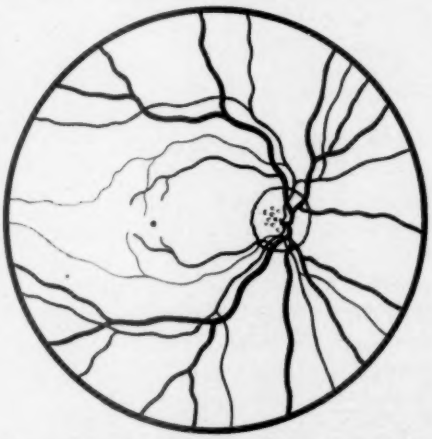

FIG. 5.—The normal fundus. Note: In making a rough sketch on a case sheet only the main four vessels need be drawn.

In examining the fundus a habitual systematic order is essential to avoid missing anything of importance. A suggested order is: the disc, the macula, the blood vessels and the retinal background.

THE OPTIC DISC

The optic disc is as individually characteristic as a finger-print and its pattern is probably only repeated in an identical twin. Indeed, the optic discs and retinal vascular distribution were criteria in settling a dispute in Switzerland to decide which two of three boys were, in fact, identical twins.

The inspection of a disc calls for a definite plan. A 'C' mnemonic is sometimes helpful:—

Colour faintly pink, pale or atrophic; *circumference*—clear-cut, blurred or absent disc-margin; *crescents* in myopia; *contour*—swelling or cupping; *circulation*—the state and distribution of the vessels; *cribrosa*, lamina, whether abnormally obvious or not visible; and *curiosities* or abnormalities such as neuroglia, pigment, hæmorrhage and so on.

Colour.—The normal disc is light-pink in colour and is relatively paler in the temporal half, which is free from vessels, than in the nasal segment in which the vessels are closely aggregated.

In *optic atrophy* the colour of the disc is altered. There are different ways of classifying optic atrophy but the following is suggested as comprehensive.

(a) *Primary*, or simple, where there has been no antecedent swelling of the nerve-head and no obvious disease of the retina causing degeneration of the ganglion walls.

The cause may be direct trauma to the nerve as in a fracture involving the apex of the orbit; demyelinating diseases; toxins such as lead, quinine; neurosyphilis (in 10 per cent. of cases in which optic atrophy is found); vascular disease such as temporal arteritis; neoplasms pressing directly upon the nerve as in the Foster-Kennedy syndrome.

The characteristic change is pallor—white, grey or bluish. The disc-margin is clear-cut, the lamina cribrosa is easily seen and there is an absence of small vessels on the surface of the disc. The disc resembles a white moon in a blood-red sky.

(b) *Secondary*.—This occurs when the ganglion-cell layer of the retina has been damaged by observable pathological processes in choroid or retina such as choroido-retinitis, primary pigmentary degeneration (retinitis pigmentosa) and so on. The appearance of the actual disc may be the same as in primary optic atrophy but the general fundus picture shows the cause to which the atrophy is the secondary effect.

(c) *Consecutive*.—This occurs when the disc has been previously choked by papillœdema which has subsided. The exudate undergoes organization and obscures the pattern of the disc with connective tissue so that the margin

is blurred, the lamina cribrosa is hidden, and the vessels are ensheathed in neuroglia and the disc appears shaggy.

(d) *Glaucomatous.*—The disc is white or pale-grey. The characteristic feature is deep cupping of the disc. The excavation extends to the very margin of the disc which is undermined so that there is an overhanging cornice or lip. The lamina cribrosa may be in evidence or may be obscured by neuroglia. The central vessels after passing through the lamina course over the floor of the cup, disappear under the overhanging cornice and reappear on the surface of the retina at the disc-margin, often apparently discontinuously with the earlier parts of the vessels which lie in the crater of the cup. The optic atrophy of glaucoma may be due to several factors: pressure on the nerve-fibres and ganglion-cells, kinking of the fibres at the lip of the cup and ischæmic degenerative changes at the nerve-head.

Circumference.—The disc-margin is usually well-defined but, where the retina is pale, the division is not sharply marked. In early papillœdema the disc-margin becomes blurred and often there is measurable swelling. In later stages, the swelling resembles a gelatinous mushroom and the margin is obliterated. In optic atrophy the disc-margin is clear-cut.

Crescent.—In myopia, the posterior pole of the eye is stretched, the retina and choroid give way at the temporal margin exposing a crescent of bare sclera the margin of which is often outlined by pigment. In high myopia the crescent may be larger than the disc and the sclera itself may be stretched and thinned to form a posterior staphyloma.

Contour.—In examining the disc in this connexion it is important that both of the examiner's eyes should be kept open and unaccommodated as if looking at a far distance and not at an object two inches away. The gallery of lenses is then rotated until a vessel near the centre of the disc is brought into focus with the highest possible plus-lens. The same vessel is then followed until it leaves the disc and is focused again. The difference, if any, in diopters gives a measure of the swelling of the disc. This should be carried out in vessels in different diameters, particularly where astigmatism is present. Three diopters are equivalent to 1 millimetre of swelling. Similarly, in *cupping* of the disc the base of the pit should be brought into focus, and then the retina adjacent to the disc.

Circulation.—The branches into which the central artery and veins divide lie in the nasal half of the disc. The arteries are bright red and the veins bluish-red. Pulsation of the veins at the disc is normal: but pulsation of the arteries is only seen in increased intra-ocular pressure, as in glaucoma. The arteries may be made to pulsate by finger-pressure on the globe during examination. Pulsation of the veins is a regular, gradual surging; but pulsation of the arteries, when the intra-ocular tension is increased beyond the systolic pressure, is seen as a jerky, flick-like emptying and filling of the arteries on the disc.

Lamina cribrosa.—The perforations of the sclera can be seen in many normal discs, particularly in the temporal segment, as small greyish oval markings in the pit or excavation of the disc. In glaucoma the perforations become very distinct.

Curiosities.—The disc may show unusual departures from the normal such as congenital holes; coloboma of the disc; hyaline bodies; foreign bodies such as a fragment of metal; as well as hæmorrhages, aneurysms and neuroglial proliferation.

THE BLOOD VESSELS

The retina is the only place in the living body in which blood vessels can be seen in the raw. The media of the eye and the tissues of the retina which support the retinal veins and arteries are transparent, and pathological changes in vessels, which elsewhere can only be inferred, are seen in the fundus as they take place.

Veins show many pathological variations such as general expansion or enlargement in polycythæmia; localized variations in calibre where they are crossed by a sclerotic artery; sheathing in periphlebitis and leukæmia; micro-aneurysms in diabetic retinopathy; new-formed vessels in the retina or on the disc; occlusion of the central vein as a terminal phase in phlebo-sclerosis and this is associated with hæmorrhages scattered to the extreme periphery of the fundus; and many rarer conditions such as angiomatosis (von Hippel-Lindau disease, a phakomatosis) in which the veins are grossly dilated, tortuous and aneurysmal.

Arteries.—An early sign of arterial disease is a loss of translucency of the vessel wall so that at a crossing an underlying vein does not show darkly through the artery. Then the reflex from the surface of an artery which is relatively taut and rigid is brighter than the surface-reflex from a normal vessel. Later, the artery may be accompanied by fibrous-looking white lines alongside its walls, a fibrotic perivasculitis strengthening the vessel against internal strain. Arteries and veins at their crossing are held in a common adventitial sheath and when an artery becomes thickened it takes up space at the expense of the vein which is narrowed and depressed. In long-standing hypertension the arteries become tortuous and appear to be narrowed in calibre. The central artery may become occluded with sudden loss of sight. The main trunk and its branches then appear as empty white cords and the retina surrounding the disc becomes pale and œdematous. In contrast to this pale retina, the macula, for a few hours or days, may appear as a cherry-red spot.

In general, changes in the retinal arteries indicate pathological changes in the walls of the systemic arteries, but high blood pressure is not always manifest in the retinal arteries and, on the other hand, profound changes in the retinal arteries may be found where the brachial blood pressure is

within normal limits. The appearance of the retinal blood vessels is a valuable sign but only one of many data to be considered in the clinical picture.

THE MACULA

The macula lutea is physiologically the most important part of the fundus as it subserves central detailed vision. Examination of the macula, particularly in aged persons in whom the pupil is contracted, often requires the pupil to be dilated with a mydriatic such as homatropine or 'paredrine' in a one per cent. solution. It is essential that a drop of eserine in 0.5 per cent. solution should be instilled after examination. Atropine should not be used as a mydriatic for purposes of fundus examination as its action cannot be countered by eserine.

The macula is less than two disc-diameters from the temporal margin of the disc. It is devoid of vessels and is often somewhat dusky in colour. There may be a bright spot at its centre.

Senile macular degeneration is responsible for 23 per cent. of cases of blindness over the age of 70. Loss of visual acuity or complete loss of vision may occur. The ophthalmoscopic appearances are fine stippling with pigment, small hæmorrhages and dot-like exudates. Gross exudation may be found over, or in a ring around, the macula and are described respectively as disciform and circinate retinitis. The remainder of the retina is often undisturbed so that the patient retains peripheral vision and is able to get about unassisted. The macula may also be damaged by direct sunlight as in looking at an eclipse, or by an electric-arc flash. In the latter case there may be a bright red hæmorrhage at the macula turning, months later, into an area of pigmentation. Some hereditary eye diseases are associated with macular changes and dysfunction. The ophthalmoscopic appearance of the macula does not always give an accurate indication of the visual acuity. Fine changes scarcely visible may produce central blindness whereas in changes much more evident useful vision may be retained.

THE EYE-GROUND

The colour of the fundus shows great variety. As the retina itself is transparent the colour depends upon the colour of the choroid and the retinal and choroidal pigment. The colour varies from bright orange-yellow to dusky red. In albinos, in whom retinal pigment is sparse, a tangled skein of choroidal vessels can be seen deep to the more orderly pattern of the retinal vessels and every variation is seen until we come to the dark races in which the retinal vessels scarcely stand out against the dark background.

Ophthalmoscopic examination of the retina shows an amazing variety of pictures of which in the space at disposal only a few can be indicated. First it should be stated that, as the retina is essentially neural, the condition of retinitis or inflammation of the retina is usually a misnomer. Retinitis, so-called, may be an inflammation of the underlying choroid which

involves the retina in secondary changes or it may be a degeneration of the retina to which the term *retinopathy* is more appropriate than the word retinitis.

Of the retinopathies, three are of prime importance: hyperpietic, renal and diabetic. In *hyperpietic retinopathy* changes in the vessels as already described are seen in the earlier stages; then small scattered hæmorrhages and small circular white exudates occur. In the final stages profuse hæmorrhages, large exudates and papillœdema (in malignant hypertension) are seen; to be followed in some cases by hæmorrhages into the vitreous and secondary glaucoma.

Renal retinopathy shows narrowing of the arteries, œdema of the retina and blurring of the margins of the disc. Flame-shaped hæmorrhages and soft masses of exudate—the 'cotton-wool patches'—are then added to the picture.

Diabetic retinopathy, which occurs particularly in long-standing cases of diabetes, is characterized by vascular changes, solid waxy-looking exudates and small punctate micro-aneurysms, which were formerly thought to be punctate hæmorrhages. There is often no clear-cut division between the various types of retinopathy; for hypertension, renal changes and diabetes may coexist.

Neoplasms.—The two commonest forms of malignant disease seen in the fundus are the retinoblastoma, formerly called glioma of the retina, and malignant melanoma of the choroid.

Finally, *retinal detachment*. This should first be examined by the indirect method to define its limits. It is typically seen as a greyish diaphanous wavy swelling upon which the retinal vessels appear as dark threads. Where there is a hole or tear the red choroid can be seen through the gap.

CONCLUSION

It may fairly be said that the clinical examination of a patient suffering from any disease, apart from a local lesion, cannot be considered to be complete without an ophthalmoscopic examination; and there is moreover the interest and fascination of 'seeing the works'.

My thanks are due to Messrs. Hamblin for figures 3 and 5, and to the Photographic Department of St. Paul's Eye Hospital, Liverpool, for figures 1, 2 and 4.

REVISION CORNER

PHANTOM LIMB

WHETHER the amputation has resulted from accident or operation, it is usual for the patient, at least for a time, to experience sensations as if the limb were still present. Such sensations may be painless or painful, but are generally more or less abnormal.

PAINLESS PHANTOM LIMB

The experiences of a minister, who had a painless phantom limb after amputation, provide a suitable clinical description.

At the age of 14 he had a mid-leg amputation and at the age of 48 he sought assistance as, ever since the operation, he had always been aware of a phantom right foot, stating that the instep and big toe were most clear and resembled the real foot although the ankle was not part of the phantom. He could 'flex and extend the foot and toes' and they were correctly placed in relation to the stump. The phantom foot was never quite normal, feeling broader than the normal foot and weather conditions affected it, so that the toes might feel crushed if it was frosty or feel immersed in moving water before rain came. He did not complain of the leg stump, which appeared normal, but continued pressure on a nerve bulb in the calf produced 'sensations' in the phantom toes.

Those who are born without digits or portions of limbs (intra-uterine amputation) never have phantom limbs, but it is true that amputation of an infant's limb may be followed by a phantom. Critchley (*L'Encéphale*, 1955, **6**, 501) reports one at the age of 3½ two years after amputation.

The story of a boy is remarkable, for as an infant he lost his right little finger and when serving in the 1914-18 War was so badly wounded in the right arm, that amputation was required. During his growing years he never had a phantom of his little finger, but after the major amputation, he had a phantom limb ending in a thumb and three fingers.

The onset is usually soon after the amputation and the disappearance is variable. General illness or trauma of the stump may cause return of a phantom.

An elderly man, who had lost the phantom connected with a thigh amputation, fractured the neck of the femur of the stump. Surgical treatment of the fracture produced a satisfactory functional result but return of the phantom.

Patients may say that the painless phantom limb feels more or less normal and gross movements may be preserved. There may even be an illusion that the hand can pass through the trunk without obstruction.

PAINFUL PHANTOM LIMB

It is noteworthy in these cases that, more often than not, the whole of the amputated portion of the limb is the phantom. The onset of pain is at the time of the appearance of the phantom and the pain is often continuous. It may be no more than an abnormal sensation—such as discomfort, an ache or cramp—or severe, being described as burning or due to great

swelling. Fatigue and sleeplessness and a tender amputation stump may exacerbate symptoms until the pain in the phantom is comparable to that of causalgia. The pain of a cardiac affection such as angina pectoris may cause symptoms in a left phantom arm. Nerve-root irritation of the cervical or lumbar plexus may produce symptoms in a phantom corresponding to those recorded in normal limbs. It is also remarkable that the victim of paralysis agitans (Parkinson's disease) may say he has a trembling in a phantom.

THE AMPUTATION STUMP

It used to be thought that the condition of the stump had an important bearing on the existence of, and symptoms arising in, a phantom limb. It is doubtful if this is really so and it is not possible to find out if there is a smaller number of phantoms arising now in amputees, who probably have better stumps than forty years ago. Sepsis in the stump was considered to be a factor of some importance in the onset and continuance of the phantom, possibly owing to inflammation of nerves in the stump. Antibiotics have practically abolished this possible cause and dispelled the idea that it was chronic sepsis which made any phantom painful. In France, however, it is considered that if the fibro-neuromas are exceptionally tender, owing to inflammation of nerve tissue in the bulb, they do play a part in the production of pain in a phantom.

It is usual to find the stump of normal appearance, free of cyanosis, œdema and trophic ulceration, but not infrequently touching the stump or placing it in some positions may increase the pain in the phantom. When pain is severe it is usual to find the stump useless, pain being dominant over adaptive functions.

THE PATHOLOGICAL PHYSIOLOGY OF PHANTOM LIMBS

Study of this condition leads to certain realizations; that:—

(a) in a painless phantom, the peripheral parts are represented, these having well-developed sensory end-organs capable of recording the body shape;
(b) phantom pain results from excessive stimulation of nerve tissue;
(c) phantom posture corresponds to that at the time of amputation, and
(d) voluntary movement in phantom fingers and toes (and less often in larger segments) is possible.

The destruction of the cortical sensory receptive mechanism in the parietal lobe causes immediate abolition of the phantom limb. It is interesting to note that recent work reveals that phantom sensation in organs other than limbs occurs after surgical removal. Although it may be tempting to think that Nelson was right in believing that the phantom fingers of his amputated arm provided a 'direct proof of the existence of the soul', the phantom is regarded today as the expression of intactness of corporeal awareness or body image.

TREATMENT

It is more likely that a painless phantom will disappear than one that is painful.

Preventive.—Phantom limbs are experienced less when the amputation is undertaken at a hospital equipped for the postoperative treatment. Unfortunately in all countries emergency operations have to be performed at the 'nearest hospital'. Ideal conditions exist when there is a staff accustomed to postoperative treatment of the amputee, both psychological and surgical. The expert bandaging, stump exercises and functional re-education, including the provision of temporary and permanent prosthesis and walking instruction, all limit complications of an amputation.

For the painless phantom limb.—Provided there is a normal stump, it is unwise to advise any form of surgery, and psychological treatment often tends to fix or increase symptoms.

For the painful phantom limb.—So large a variety of treatments to the stump, to nerves and to portions of the central nervous system has attracted attention that a decision to operate on the brain (leucotomy or on sensory cortex), on the spinal cord or nerve roots should be undertaken only after very serious consideration.

Obviously, a stump with tender bone or nerve bulbs and periodic infection should be reconstructed, but reconstruction has no place in dealing with the pain of a phantom limb. Local injections, repeated percussion, electrical treatment or shortening of nerves with removal of bulbs sometimes relieves pain. It is difficult to understand the mode of action of sympathectomy in these cases; although results must be considered variable, some patients have been relieved of pain.

A patient having a painless or painful phantom limb should not be abandoned by his doctor, but should be provided with all the mental and physical help available, difficult though this may often be.

ST. J. D. BUXTON, M.B., F.R.C.S.
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THE PLASMA PROTEINS

THE plasma proteins comprise albumin, globulin and fibrinogen and amount in total to some 6 to 8 g. per 100 ml. of plasma. With the exception of fibrinogen, which must be estimated in plasma, determinations are usually carried out on serum, as the use of anticoagulants tends to draw water from the cells, to dilute the plasma, and consequently to give results lower than the true value in circulating plasma.

FRACTIONS AND ORIGIN

By 'salting-out' techniques the total protein content can be broken down into various fractions: 3.5 to 5 g. per 100 ml. albumin, 1.5 to 3 g. per 100 ml.

globulin, and from 0.2 to 0.4 g. per ml. fibrinogen. The ratio of albumin to globulin is often quoted, but in my opinion it is of little value. The absolute values of albumin and globulin are much more helpful and the important figures are the *minimum* value for albumin and the *maximum* value for globulin: any value of albumin above 3.5 g. per 100 ml. is probably normal and similarly any value of globulin below about 3 g. per 100 ml. is within the normal range.

In understanding the significance of changes in protein values in disease, the source from which the proteins are produced should be considered. The albumin and fibrinogen are entirely produced in the liver, and therefore parenchymal damage to the liver is liable to produce low values for these constituents. Globulin has a much broader source, being produced chiefly in the reticulo-endothelial system and the lymphatic tissues: hence a raised value for globulin is often met with in infections and in various forms of enlargement of the lymph glands, including lymphatic leukæmia, but this rise is not diagnostic of any specific condition.

The proteins of the plasma are not inert substances; they undergo rapid metabolic changes and are renewed and replaced very frequently under normal conditions.

So far globulin has been referred to as though it were one substance, but more recent techniques and comparatively simple applications such as paper electrophoresis have shown that 'globulin' is a very complex mixture of proteins: the globulin fractions thus isolated are described as α_1 and α_2, β and γ globulins. For ordinary clinical purposes a simple naked-eye inspection of the electrophoretic paper strip and description of any increase or decrease of one of the fractions, plus an indication of any abnormal protein present, are more helpful than any attempt to elaborate values for all the globulin fractions.

THE PLASMA PROTEINS IN DISEASE

In *parenchymatous liver disease* there is often a fall in the albumin with a rise in globulin, usually shown on the paper strip as a diffuse increase in the γ-globulin region. Fibrinogen may also be diminished in liver disease.

Afibrinogenæmia or hypofibrinogenæmia is sometimes met with as an acute post-partum condition, and its recognition is necessary for appropriate therapy. Rapid chemical methods are available for fibrinogen estimation. Congenital afibrinogenæmia causing a form of hæmorrhagic disorder also occurs, but is an exceedingly rare condition.

In *chronic nephritis*, particularly in the nephrotic stage, the gross loss of albumin in the urine often produces a low serum-albumin figure: this is usually associated with an absolute increase in globulin, particularly of the α_2 and γ fractions.

Multiple myelomatosis is characteristically associated with a very high globulin content of the serum, and excretion of Bence-Jones protein in the urine, but either of these findings may be absent. The presence of an abnor-

mality of serum protein is common, and shows on electrophoresis as a sharp band, unlike the diffuse increase in γ-globulin found in liver disease: this band usually occurs in the γ-globulin region, although it may sometimes occur elsewhere, or be absent.

Occasionally an abnormal protein is found which is called '*cryoglobulin*' on account of its separating from serum when this is cooled, and recently attention has been drawn to other abnormal globulins of very large molecular weight—the so-called 'macroglobulins'. Both these appear on electrophoresis as fairly sharp bands similar to the myeloma protein. They cannot be identified with certainty except by the use of an ultra-centrifuge but, as their specific identification does not lead to any more definite therapy, this does not matter seriously.

A high serum globulin content is also often met with in *sarcoidosis*, and in some of the collagen diseases, especially systemic lupus erythematosus.

The rare condition of *congenital agammaglobulinæmia*, in which a baby may have had a series of repeated infections is recognized by the continuing complete absence of γ-globulin from an electrophoretic strip: a low content of γ-globulin, however, may occasionally occur temporarily as an unusual response to infection.

SUMMARY

It cannot be said that estimation of the serum proteins often gives a definite diagnosis of the cause of a patient's illness, but their investigation not infrequently gives a pointer to the condition to be specifically looked for, and is often of confirmatory diagnostic value.

E. N. ALLOTT, D.M., F.R.C.P.
Director, Lewisham Group Laboratory.

NOTES AND QUERIES

Transport of Spinal Injuries

QUERY.—What is the correct first-aid treatment for suspected fracture of the spine? Originally I was taught that such a case should be carried face down in the prone position. I note, however, that the Civil Defence First-Aid Manual states categorically that the patient must be transported on his back.

REPLY.—Like most surgeons my experience of first-aid treatment of serious injuries at the accident site is limited. The first problem is the safe extraction of such injured from the debris of their accident: for example, from the smashed and badly crushed interior of a car or from the cab of a lorry—before any sort of examination is possible to ascertain the nature of their injuries. Fortunately such injured people are often unconscious during what is a major operation. At this stage care should be exercised in preventing hyperextension or acute flexion of the spine. Ambulance crews have told me that they generally get over this difficulty by pulling the victims out either by their feet or by their shoulders. I have no personal experience of this problem.

On several occasions I have given roadside first-aid to very seriously injured people who have been thrown clear of the accident debris. It is remarkable how quietly they lie in the position in which they have fallen, with their muscles in spasm protecting the underlying bone and joint injuries. Since any added movement immediately causes a fresh spasm of pain, I have carried out my examination in such conditions leaving the victims in the original position in which they had fallen and restricted my activities to wound cover alone until the arrival of the ambulance.

The arrival of the ambulance with its stretcher

presents the next problem. How to lift patients with suspected spinal injuries on to the stretcher? This is the move that has caused considerable confusion in the instructions contained in first-aid manuals. If this *lift* is carried out by two attendants—one at the victim's knees and the other at the shoulders—hyperflexion of the spine can occur with obvious danger to the cord. The old manuals therefore advocated turning the patient on his face before lifting him on to the stretcher. It is now recognized that the same type of two-attendant lift hyperextends the spine, itself a recognized danger to the cord in certain types of fracture-dislocation with locked articular facets. The safest method is to lift the patient in the position in which he is found without preliminary moves, and on to the stretcher brought as closely to his side as possible.

As to the position of the patient on the stretcher during transport, *this should be on the back with face up*. This position allows adequate splinting of associated limb injuries, easy breathing and clear observation of the injured patient by the ambulance crew during transport. I once observed the condition of a patient immediately on his arrival at hospital after he had been transported face down on the stretcher (because it was thought that he had a spinal fracture). The lesions were subsequently shown to be a compound fracture of the femur and multiple rib fractures, with facial injuries. On his arrival at the hospital his respiratory difficulties were extreme and he was in a serious general shocked condition.

As a method for first-aiders the 'face down' position both for lifting on to the stretcher and for subsequent transport on the stretcher in the ambulance is to be condemned.

W. GISSANE, CH.M., F.R.C.S.

Repeated Fœtal Abnormalities

QUERY.—A married woman, aged 22, has consulted me on the advisability of starting a fourth pregnancy. She has had no past illnesses and her husband is also well. Their Wassermann reactions are negative and the wife is Rhesus-positive. Their first baby had a congenital heart, with malrotation of the gut, and died a few months after birth. The second baby had a normal delivery and is healthy with no known abnormality. The third baby died three days after birth—meningocele with paraplegia, and hydrocephalus.

They would like to have another child but are scared that they will have another abnormality. What are the chances of this?

REPLY.—The question as to the recurrence of fœtal abnormality in a family is still a difficult one to answer. The history given here is not complete; for example, if the mother had rubella in the first pregnancy an immediate explanation for one of the unfortunate events would be given. Similarly, it would be valuable to know if the question of consanguinity in the marriage arises.

In general, it seems to be quite definite that the chance of recurrence of some type of fœtal abnormality is more likely in a family where it has previously occurred. Murphy estimated the chances as being twenty-four times greater than in the general population. Penrose found sixteen cases of deformity in 207 families where one baby had previously been born abnormal. The types of deformity stated in the case in question being dissimilar and of a recessive type would not make one advise against further children, especially as the mother is young, but it is difficult to give statistical odds on the chances.

KENNETH BOWES, M.D., M.S., F.R.C.S., F.R.C.O.G.

Dupuytren's Contracture

QUERY (from a reader in South Africa).—My wife, aged 34 years, has suffered from Dupuytren's contracture for about four years. There are marked contractions of both thenar and hypothenar eminences resulting in pain and weakness on grasping objects. She had one course of x-ray therapy in 1954, consisting of six weekly treatments of 100r each. There was marked improvement symptomatically. In March 1956, she had four treatments of 100r each, without any improvement. Her mother and paternal grandfather had marked Dupuytren's contracture. Is there any further treatment available?

REPLY.—This query presents certain unusual features. First, Dupuytren's contracture is unusual in a woman. Secondly, it is unusual to start at the age of thirty, and thirdly, involvement of the thenar eminence is extremely rare. Pain is an unusual feature in Dupuytren's contracture, and weakness in gripping is rarely complained of.

It is not possible to give any useful advice in a case such as this because of the obvious anomalous features. Ordinarily the treatment is surgical. X-rays are considered by some to be of transitory benefit but in the presence of deformity the only treatment seriously to be considered is either fasciotomy, that is to say division of the thickened bands causing the contracture, or excision of these bands together with the surrounding palmar fascia.

RONALD FURLONG, M.B., F.R.C.S.

Coloptosis

QUERY.—What does one do for a woman patient of 32 who has suffered mediocre health for the

past five years, and in whom cholecystography follow-up shows a U-shaped transverse colon sinking deeply into the pelvis with evidence of spasticity? She is asthenic, slightly constipated, and mildly neurotic.

REPLY.—It is not quite evident how cholecystography has demonstrated the transverse colon, and before advising treatment it would be wise to have a barium enema carried out to outline fully its position and to exclude any organic abnormalities. A low U-shaped transverse colon is unlikely itself to be causing any symptoms by virtue of its position, but if there is associated diverticulitis or colitis this might cause abdominal discomfort and perhaps some general ill health. It is generally agreed that any benefits which follow abdominal exercises, massage or the wearing of special belts for a dropped or low colon are due to suggestion and not to any direct effect upon the position of the bowel. Asthenia and constipation are rarely, if ever, directly due to coloptosis and it is usually wise in treatment to direct the patient's attention away from her bowel and to more general causes of her symptoms.

One of the most usual causes of long-continued mediocre health is anxiety, and if the patient is mildly neurotic it would seem best to treat this condition and ignore the position of the colon and the slight constipation. Such treatment would, of course, involve discussion and explanation of psychological causes of exhaustion, and an attempt to help the patient to adapt herself to her life and to her symptoms. Sedatives and help with sleep would in this case be more likely to help than any laxatives, 'tonics' or special diets.

THOMAS HUNT, D.M., F.R.C.P.

Morphine and Urinary Secretion

QUERY.—Is there any substantial evidence that morphine decreases urinary output by the kidneys, as opposed to causing retention of urine within the bladder? I have been advised against the use of morphine in eclampsia and pre-eclampsia on these grounds.

REPLY.—De Bodo (*J. Pharmacol.*, 1944, **82**, 74) has shown that morphine decreases urinary secretion by causing release of antidiuretic hormone. It also increases excretion of oxytocin, and for these two reasons its use is contraindicated in pre-eclampsia.

PROFESSOR G. M. BULL, M.D., F.R.C.P.

Thrombophlebitis and Phlebothrombosis

QUERY.—My impression is that there is no consistent policy in the management of venous thrombosis. The distinction between thrombophlebitis and phlebothrombosis is too hard and fast. This is recalled by some recent cases:—

A patient with a superficial thrombophlebitis in a varicose vein was treated with rest and penicillin. The thrombosis continued to extend and I asked for admission to hospital. This was refused and the patient developed a pulmonary embolus. An exactly similar case was admitted to hospital but was not put on anticoagulants until, while in hospital, she developed multiple pulmonary emboli. A third case had superficial venous thrombosis of the left leg near the ankle. She was put on partial bed rest for ten days, after which she was allowed to be ambulant. After five days on her feet she developed a fatal pulmonary embolus, apparently from deep veins in the right calf. At the time of allowing her up, there was no clinical evidence of any lesion in this area.

A final case, which I saw recently, presented a few days after childbirth with superficial venous thromboses affecting the left calf and in both thighs. She was admitted to hospital but no anticoagulant treatment was given. The patient did well. The obstetrician concerned stated that he never treated such cases with anticoagulants.

The problem of venous thrombosis is a common one in general practice. I have decided on the following policy and would appreciate your comments:—(1) If a limited area is involved, I keep the patient ambulant, and provide support and give penicillin. (2) If the lesion extends, or is at all extensive, I refer the patient to hospital for anticoagulant therapy. (3) If this is refused, and hospitals do not willingly accept this type of case, then one has no alternative but to keep the patient under constant review for possible extension of the superficial lesion or the concurrent development of deep thrombosis.

From my experience it is apparent that this policy will not always prevent the development of pulmonary emboli, and I consider that, ideally, anticoagulant therapy should be given in all cases. I would, however, appreciate the comments of an experienced physician.

REPLY.—The points raised in this query are indeed cogent. The distinction between thrombophlebitis and phlebothrombosis is not hard and fast, and often, as the reader intimates, the two conditions merge. In clinical practice most cases fall midway between the two ends of the spectrum. In many instances, venous thromboses clear up spontaneously without further extension and without causing pulmonary emboli: an example is the patient mentioned above who developed superficial thrombosis

after childbirth. In other instances, where the inflammatory component is not great, the thrombosis may extend and pulmonary emboli occur as exemplified in the first three cases cited above.

The policy suggested is sound and in keeping with modern practice. Lack of marked inflammation, extension of the disease, and involvement of more than one vein all call for anticoagulant therapy. Until this is more widely appreciated there will continue to be cases of pulmonary emboli, some of which will be fatal.

RICHARD BAYLISS, M.D., F.R.C.P.

Treatment of Lambliasis

QUERY.—What is the currently recommended treatment for lambliasis in a small child (aged three)? There is a history of recurrent diarrhœa, and cysts found in the fæces.

REPLY.—Mepacrine, 0.05 g. twice daily after meals for five days, is the recommended dosage for a child of three. The bitter taste of the tablets can be minimized by giving them crushed and mixed with honey.

D. R. SEATON, M.B., M.R.C.P.

Non-spermicidal Lubricant

QUERY.—I have been asked by a young couple to recommend a non-spermicidal lubricant to use in order to facilitate intercourse. Is 'KY' jelly suitable or, if not, could you tell me what to suggest?

REPLY.—There are various non-spermicidal lubricants on the market. 'KY' jelly is entirely suitable although some object to its rather penetrating odour. Alternative preparations which can be recommended are 'lubafax' and 'prentif lubricant jelly'. These preparations are all water-soluble, which is a great advantage over a greasy preparation, and all would appear to be entirely non-toxic.

JOSEPHINE BARNES, D.M., F.R.C.S., F.R.C.O.G.

PRACTICAL NOTES

Nystatin in Moniliasis

THE results of the use of nystatin in 122 cases of moniliasis are reported by E. T. Wright *et al.* (*Journal of the American Medical Association*, January 12, 1957, **163**, 92). Nystatin was used in the form of ointments, solutions, powder, troches, capsules, suppositories and jelly. The ointment and gel consisted of a plasticized petrolatum base containing 5000 to 200,000 units of nystatin per gramme of ointment base. Two types of solution, containing 5000 to 100,000 units per ml., were used. One was propylene glycol solution, and the other contained 2% procaine hydrochloride and 0.25% polysorbate 80. The latter solution was prepared both with and without 2.5 mg. of hydrocortisone per ml. The powder contained 175,000 units per teaspoon. Each troche contained 2000 units; in addition, some of them contained 2.5 mg. of neomycin sulphate and 0.25 mg. of gramicidin. The capsules and tablets that were used as troches and suppositories contained 125,000 to 500,000 units. The suppositories for vaginal use contained 10,000 to 100,000 units, and some contained the same amount of neomycin and gramicidin as the troches.

Of the 42 patients with oral moniliasis, 19 showed an excellent response and 22 a good response. Of the 17 cases of vaginal moniliasis, nine showed an excellent response and eight a good response. Of the 63 patients with cutaneous moniliasis, the results were excellent in 25 and good in 34. In the 16 patients with cutaneous moniliasis who were treated with the solution containing hydrocortisone, the treatment period was almost 50% shorter than in those treated with the solution containing no hydrocortisone. In the treatment of intertriginous infections the solution was found more satisfactory than the ointment. No side-effects were observed. The period of treatment ranged from three days to one month.

Benzathine Penicillin in Syphilis

'A SINGLE injection of 2.5 million units of benzathine penicillin G, in early infectious syphilis, produces results equal, if not superior, to those obtained with schedules employing 4.8 million units of procaine penicillin and aluminium monostearate', according to C. A. Smith and his colleagues (*Bulletin of World Health Organization*, 1956, **15**, 1087). In the series of cases upon which their report is based they have had no failures among 52 patients treated for sero-negative primary syphilis, 27 of whom have been followed for more than a year, and 11 for more than two years. Among 67 patients with sero-positive primary syphilis, two (4%) have required further treatment: one for serological relapse and one for reinfection. Of 155 patients treated for secondary syphilis, 90 of whom have been observed for more than a year, and 37 for more than two years, the cumulative re-treatment rate was 5.5% (0.9% serological or clinical

failure, and 4.6% reinfection). The sero-negativity rates for the three stages two years after treatment are: 100% for sero-negative primary, 96% for sero-positive primary, and 94.5% for secondary syphilis. On the other hand, preliminary data suggest that a single injection of 2.4 or 2.5 mega units of benzathine penicillin may be inadequate for the treatment of asymptomatic neurosyphilis. Thus, by the eighteenth month following treatment, 21% of the patients with asymptomatic neurosyphilis treated with benzathine penicillin G had relapsed, compared with 10.5% of those treated with other penicillin G preparations.

Acetazolamide in Pre-Eclamptic Toxæmia

'ACETAZOLAMIDE ["diamox"] is a useful adjuvant to the treatment of pre-eclamptic toxæmia', according to Raymond Shanahan (*Journal of the Irish Medical Association*, February 1957, **40**, 57). This conclusion is based upon the findings in 22 patients, including nine primiparæ. Patients were accepted for inclusion in the investigation if the blood pressure remained above 130/90 mm. Hg after two days' bed rest in hospital. All the patients had an initial period in hospital before acetazolamide was administered. If the nett daily fluid loss following acetazolamide was increased by more than 420 ml., compared with the control period preceding its use, the result was classified as 'good'. If the nett loss was increased by 280 to 420 ml., the result was assessed as 'fair'. The daily dose of acetazolamide was 250 mg. It is recommended that this dosage be maintained until the response ceases. After two days without treatment, administration is started again, and this cycle is continued for the duration of pregnancy. In this series, 'good' results were obtained in 11 patients, including five primiparæ, and 'fair' results in two (one primipara). There was no significant alteration in blood pressure, even in those who had a satisfactory diuresis. No side-effects were observed. Two stillbirths occurred in the series, but each was in a patient with a 'very severe toxæmia'.

Chlorpromazine in Malignant Disease

THE effect of oral chlorpromazine as an adjunct in the relief of pain has been studied in 76 patients by J. W. Dundee (*British Journal of Anæsthesia*, January 1957, **29**, 28). 'Very good results' were obtained in subjects with malignant disease, but 'not so good results' in other type of pains. The series included 38 patients with malignant disease, 25 with 'nerve' pains, and six with osteoarthritis. Chlorpromazine by itself possessed little analgesic value, but in conjunction with analgesics it produced satisfactory relief of pain in 32 (89%) of the patients with malignant disease. The initial daily dose of chlorpromazine was 25 mg., which was gradually increased, if necessary, to a total of 50 mg. four-hourly during the day (250 mg. daily). This total was never exceeded. The best results were obtained with a combination of chlorpromazine and levorphan. Codeine compound tablets B.P. combined with chlorpromazine gave good results in patients with moderately severe pain, and often proved more efficacious and produced less side-effects than the more powerful analgesics. Side-effects due to chlorpromazine were encountered in about two-thirds of the patients, but in only two cases were these serious enough to require discontinuation of treatment. Attention is drawn to the fact that in 10 patients pyrexia occurred during the second week of treatment, and that one of these patients subsequently became jaundiced. It is therefore recommended that serum bilirubin and alkaline phosphatase determinations and leucocyte counts be carried out at frequent intervals in patients who are having prolonged treatment with chlorpromazine.

'Nitromin' in Malignant Disease

THE effect of a nitrogen mustard analogue—nitrogen mustard -N-oxide ('nitromin')—in 19 cases of advanced malignant disease or reticuloses has been studied by B. A. Stoll (*Medical Journal of Australia*, December 15, 1956, **ii**, 882). This analogue is said to have the advantage of a relatively high ratio of tumour depression to marrow depression. Further, complications of nausea and vomiting are said to be minimal. There were two cases of malignant melanoma and two cases of lymphosarcoma in the series, and all four showed temporary regression of tumour masses during treatment. There was temporary regression in three of the 10 cases of advanced carcinoma. The one case of embryoma of the kidney showed no response. There was no response in the two cases of lymphosarcoma, and only a partial response in the two cases of Hodgkin's disease. The dose, orally or intravenously, is 1 mg. per kg. body weight. The usual dose for adults was 50 mg., dissolved in 50 ml. of saline, daily, either intravenously or orally at least three hours after a meal or the last thing at night. A full course generally comprises 750 mg. over a period of fifteen to twenty days. Response is often apparent after the first week of treatment.

Hypnosis for Hyperemesis Gravidarum

TWELVE cases of hyperemesis gravidarum suc-

cessfully treated with hypnosis are reported by S. W. Giorlando and R. F. Mascola (*American Journal of Obstetrics and Gynecology*, February 1957, **73**, 444). All were severe cases and all benefited from this treatment. The only pregnancy which did not result in a normal baby was that in a woman who had a spontaneous abortion at 12 weeks. Her previous pregnancy had also terminated in a spontaneous abortion—at 8 weeks. In nine cases there was relief of vomiting after one session, two patients required two sessions, and one required three sessions. Eight patients had one or more additional monthly sessions of hypnosis. Details are given of one case in which vomiting persisted after admission to hospital in spite of intravenous fluids and barbiturates. 'Strong consideration' was being given to the possibility of therapeutic abortion when, 'in desperation', it was decided to try hypnosis. She was able to retain fluids on the same day as the first session of hypnosis, and intravenous fluids were stopped immediately. Further hypnosis sessions were given as a prophylactic measure, and pregnancy thereafter pursued a normal course. The view is expressed that the methods of hypnosis in such cases are 'simple and can be mastered by any physician'.

Psoriasis and Arthritis

THREE groups of patients have been analysed by V. Wright (*British Journal of Dermatology*, January 1957, **69**, 1): 42 with psoriasis and arthritis, 55 with rheumatoid arthritis only (all of these had a positive Waaler-Rose differential agglutination test [D.A.T.]), and 310 with psoriasis only. Of the first group, eight with arthritis other than 'erosive arthritis' (the term 'erosive arthritis' is used in preference to rheumatoid arthritis so that the issue may not be prejudged) showed no feature which was not explicable on the chance coincidence of the two diseases. Of the 34 patients with erosive arthritis and psoriasis, 94% had a negative D.A.T. This is taken to suggest that the combination of psoriasis and erosive arthritis is more than coincidence of two common diseases, since the D.A.T. was positive in over 80% of patients with rheumatoid arthritis. 'It suggests that in those with a negative D.A.T. the arthritis either is modified by the psoriasis, or more probably is a distinct entity'. The finding of tendon sheath effusions and subcutaneous nodules (both classical manifestations of rheumatoid arthritis) in only one patient in the series—one of the two with a positive D.A.T.—'lends weight to the suggestion that these two were true rheumatoid patients, while the others formed a distinct group'. Two other points of interest brought out by this investigation are that of the 34 patients with erosive arthritis, 18 were men and 16 were women (whereas both rheumatoid arthritis and psoriasis, occurring singly, are commoner in women), and that the nails were involved in 87% of the patients with erosive arthritis, compared with only 18% of those with uncomplicated psoriasis.

Urinary Calculi

IN a review of the pathogenesis of urinary calculus formation, Mary G. McGeown and G. M. Bull (*British Medical Bulletin*, January 1957, **13**, 53) conclude that 'the current hypothesis that stone formation is due to a deficiency of some substance which holds calcium in solution in normal urine, or to an excess of some substance with which calcium forms an insoluble complex, cannot be regarded as proved'. They consider that there is a relationship between hypercalciuria and stone formation, and that in every case of renal calculus the possibility of hyperparathyroidism, with its accompanying hypercalciuria, should be considered. They report that of 76 patients who have been investigated from this point of view, 28 have been selected for exploration for parathyroid tumours. In the 15 cases so far operated on, six tumours and four glands with histological hypertrophy have been found. The view is expressed that there is no direct evidence that infection plays any essential part in the initiation of calculi, although it seems probable that it may encourage the growth of calculi in those already predisposed to them. The prophylaxis against recurrences of calculi after surgical removal rests upon the maintenance of a high fluid intake, and the treatment of coexisting urinary infection. A high fluid intake is particularly important in the evening—to prevent a concentrated night urine.

Clubbing of the Fingers

ANALYSIS of the clinical findings in a series of 27 patients with drumstick clubbing of the fingers, who attended the department of thoracic medicine, St. Thomas's Hospital, for a variety of respiratory ailments, failed to yield a common clinical denominator which might illuminate this association with lung disorders, according to L. Cudkowicz and D. G. Wraith (*British Journal of Tuberculosis and Diseases of the Chest*, January 1957, **51**, 14). In this series not one single factor emerged which was common to all patients. This applied to age, sex, history, physical signs in lungs or heart, pulse pressure, chest radiography, bronchography, electrocardiography, respiratory function tests, hæmoglobin values, and arterial oxygen saturations. This absence of a common clinical denominator

is taken to indicate the presence of an additional anomaly, and this, it is suggested, may be the formation of pre-capillary broncho-pulmonary anastomoses in abnormal lobes. Such anastomoses have been noted near lung cancers associated with painful clubbing, and it is known that clubbing disappears after excision of small lung tumours and of arteriovenous aneurysms of the lung. In three patients in the present series bilateral pre-capillary broncho-pulmonary anastomoses were associated with pulmonary hypertension. The mechanism whereby such anastomoses influence the genesis of clubbing remains a matter of conjecture.

Vitamin D Anæmia

In reporting four cases of unexplained anæmia in adults which turned out to be the result of vitamin D intoxication, W. B. Scharfman and S. Propp (*New England Journal of Medicine*, December 27, 1956, **255**, 1207) express the opinion that 'at present there seems little justification for the therapeutic use of vitamin D in a wide variety of conditions such as arthritis, allergic diseases such as asthma and pollinosis, psoriasis, acne, sarcoid and trichinosis'. In all four cases recorded the intake of vitamin D had been between 50,000 and 150,000 units daily for several years. The anæmia was uniformly normochromic and normocytic, and the hæmoglobin level varied from 8.3 to 10.75 g. per 100 ml. All four patients had varying degrees of renal failure attributed to vitamin D intoxication. The anæmia was considered to be due to the azotæmia resulting from the renal failure, but 'a direct toxic effect on the bone marrow cannot be excluded'. Treatment consists of immediate stoppage of vitamin D administration, and the administration of a low-calcium diet and a high-fluid intake. Transfusion was not required in any of the cases recorded here.

Cortisone Eye-drops

'A simple suspension of cortisone acetate powder as received from the manufacturers is not suitable for use as eye-drops', according to J. Flitcroft and M. E. Birchall (*Pharmaceutical Journal*, February 2, 1957, **178**, 79). An 'elegant dispersion', however, can be obtained by the use of 'unemul', which is described as a 'smooth gelatinous form of hydrated aluminium oxide with emulsifying, wetting and suspending properties'. Finely ground cortisone acetate is triturated thoroughly with an equal proportion of 'unemul' until a smooth paste is produced. Benzalkonium chloride (0.02%), prepared by diluting a 1% aqueous solution kept for ophthalmic use, is used as the bactericide, and methylethylcellulose (0.5%), prepared from a 20% stock paste, is included as an auxiliary suspending agent. Sodium chloride, dissolved in a suitable quantity of distilled water, is then added, and, finally, the whole is made up to volume. The formula is therefore as follows:—

Cortisone acetate	1
'Unemul'	1
Benzalkonium chloride	0.02
Methylethylcellulose	0.05
Sodium chloride	0.75
Distilled water	to 100

The product is described as 'a very fine suspension, the consistency of a thin milk, which is non-irritating to the eye and is not liable to crystal growth'. Cortisone acetate, finely powdered and triturated with its own weight of 'unemul', may be stored in a tightly closed container for up to about forty-eight hours before use, when it will be readily 'wetted' by water. If this stock dispersion is stored for any longer period, the eye-drops in which it is used tend to show crystal growth after a few days.

Silver Nitrate Stains

The following solution is said by D. J. Steward (*British Dental Journal*, February 19, 1957, **102**, 143) to be 'very effective' in the removal of silver nitrate stains:—

Bichloride of mercury	10 parts
Ammonium chloride	10 parts
Distilled water	80 parts

The solution is 'equally effective either on the skin or on fabric'. The stain is rubbed briskly with gauze soaked in the solution, and the area is then rinsed in cold water.

Spasmodic Cough and Hiatus Hernia

A violent fit of coughing on lying down is described by Ch. Debray and J. P. Hardouin (*Presse Médicale*, February 2, 1957, **65**, 207) as an important diagnostic symptom of hiatus hernia. The usual story is that the patient gets off to sleep quite easily, but is wakened up, usually in the small hours of the morning, by a violent, spasmodic fit of coughing, which compels him to sit up in bed to obtain relief. The bout usually lasts for only a few minutes, and the patient then settles down to sleep for the rest of the night. It is not accompanied by any expectoration. Not infrequently it is accompanied by heartburn and waterbrash. Patients who are subject to this spasmodic cough often find that one particular position in bed tends to bring it on. Thus, some are only subject to it when they lie on the back, whilst others experience it when they lie on either the right or the left side. The cough is attributed to regurgitation of the gastric contents irritating the glottis.

REVIEWS OF BOOKS

Symposium of Tuberculosis. Edited by F. R. G. HEAF, M.D., F.R.C.P. London: Cassell and Co. Ltd., 1957. Pp. xvi and 755. Figures 54, plates 78. Price £5 5*s*.

ALTHOUGH it will be valuable to the tuberculosis worker in Britain, clearly Professor Heaf has edited this book with a much wider public in mind: in areas of the Commonwealth and the Colonies where tuberculosis control is less established. He implies this aim in his foreword and the dust cover refers to 'countries where the tuberculosis morbidity and mortality rates remain high'. This perhaps is one reason for giving detailed mention to some methods of treatment, for instance artificial pneumothorax, which have lost popularity in this country. Although the indications and techniques of active treatment are well covered on the whole (very little is said, however, about methods of assessing respiratory function, and the treatment of tuberculous meningitis is scantily dealt with; e.g. there is no mention of isoniazid), they occupy only four chapters—including those on non-respiratory and children's tuberculosis—out of the thirteen. There is no section on pathology as such. The construction is therefore different from that of most books on tuberculosis and is exceptional in its detailed attention to the over-all picture.

Naturally, such a symposium could not be compiled without including the personal views of the collaborators (possibly most obvious in the chapter on non-respiratory tuberculosis), but generally they will be found balanced and acceptable. The admirably factual chapter on tuberculosis in industry might have been improved by a discussion on methods of combating the disease in this field. The introduction, which the editor himself writes, is of great interest as a summary of the conclusions of one who must be unique in his experience of the tuberculosis problem in so many countries. The short 'plan of approach' which occupies some three pages towards the end of this introduction gives a ground plan for anyone starting to assess the problem in a community. This is a book which physicians interested in public health or tuberculosis anywhere ought to possess and study.

Modern Trends in Geriatrics. Edited by WILLIAM HOBSON, M.D., D.P.H. London: Butterworth & Co. (Publishers) Ltd., 1956. Pp. vii and 422. Figures 68. Price 72*s*. 6*d*.

THIS symposium deals with a wide variety of subjects of practical importance in the treatment of the elderly. Some of the outstanding contributions are: 'Arteriosclerosis and Hypertension' by Dr. F. H. Smirk, 'Chronic Bronchitis' by Dr. F. J. Flint, and 'Orthopædic Surgery' by Mr. Cecil Flemming. A summary of the therapeutic agents used in the treatment of the common conditions encountered in the elderly is given by Professor G. M. Wilson. Dr. J. H. Sheldon's account of 'Problems in the Home Care of the Elderly' is most stimulating and indicates the need for a more careful clinical investigation into the common causes of disability in old age. Those responsible for the future planning of the geriatric services will find much useful advice in Dr. W. Morton's chapter on hospital care.

Professor Hobson and the other contributors are to be congratulated on producing a book which will be of great interest to general practitioners, hospital physicians, medical officers of health and administrative medical officers.

Pulmonary Emphysema. Edited by ALVAN L. BARACH, M.D., and HYLAN A. BICKERMAN, M.D. Baltimore: Williams & Wilkins Co.; London: Baillière, Tindall & Cox, 1956. Pp. x and 545. Illustrated. Price 80*s*.

THIS is certainly the most comprehensive book that has been written on this subject. It falls into two halves. In the first there are eight chapters on the causes and on the management of emphysema, as carried out at the Presbyterian Hospital, New York, by the editors and Dr. Gustav Beck. The relative lack of emphasis on chronic bronchitis as the forerunner of emphysema may surprise English readers, although full emphasis is given to the importance of exacerbations of infection in causing respiratory failure. The importance of using oxygen with caution to avoid undue respiratory depression is stressed. There is naturally a good deal about the use of helium mixtures, positive-pressure breathing and the various machines for assisting both respiration and cough for which Dr. Barach is well known, and a whole chapter, perhaps rather uncritical, on breathing exercises and other methods to 'restore' diaphragmatic function. The use of bronchodilatation, postural drainage and adrenal hormones is fully discussed but again with rather more enthusiastic claims for success than can readily be accepted by those with experience of the intractable cases which are not infrequent. The second half of the book contains seven chapters on various aspects of the disturbances of pulmonary function encountered in emphysema, written by acknowledged experts, but in

a manner which is easy to follow. There are also chapters on the treatment of bronchial infection and on various surgical procedures—which are not considered to be effective except for resection of localized overdistended bullæ.

This book will be a valued addition to the shelves of the many doctors who are becoming concerned with the fascinating etiological, functional and therapeutic problems presented by emphysema. For the busy practitioner the practical chapters are too verbose and optimistic whilst much of the theory is as yet irrelevant to practice. The bibliography, although almost exclusively American and British, is extensive.

Outline of Fractures. By JOHN CRAWFORD ADAMS, M.D., F.R.C.S. Edinburgh: E. & S. Livingstone Ltd., 1957. Pp. vii and 248. Figures 218. Price 27*s.* 6*d.*

MR. ADAMS has followed up his excellent 'Outline of Orthopædics' by a companion work on fractures. Every word is carefully selected so that with remarkable conciseness one is given a very readable compendium. It will prove a valuable guide not only to senior medical students but, equally important, to general practitioners for, as the author states, the latter 'must know upon what evidence he should suspect and recognize a fracture; he should know the general principles of treatment so that he may advise his patients intelligently in the intervals between their visits to the fracture clinic; and he should know the complications that are liable to arise'. A copy should be in every hospital casualty department: a worthy companion to more voluminous works. A feature of particular delight is the clarity, simplicity and practical value of the illustrations.

New Bases of Electrocardiography. By DEMETRIO SODI-PALLARES, M.D., with the collaboration of ROYALL M. CALDER, M.D. London: Henry Kimpton, 1956. Pp. 727. Figures 523. Price £6 15*s.*

IN the opinion of the reviewer, this is the most successful attempt which has yet been made in the English language to remove clinical electrocardiography from its still mainly empiric position and set it on a scientific footing. The author is particularly well qualified to write such a treatise and has contributed much that is original to the subject. He was the first to record cavity potential from the human left ventricle and has, in fact, devoted a whole chapter to intracavity recordings.

In such a short review it is difficult to single out particular sections for special mention, but the description of cardiac infarction is certainly outstanding, and a fascinating account of the activation process in the human heart is given. There is also a good summary of present knowledge concerning vectorcardiography. Perhaps the most valuable part of the work is the appendix, in which the author has drawn together from widely scattered sources many of the mathematical formulæ used in electrocardiography and has explained their derivation and practical application. On the debit side, although nearly one thousand references are listed all too few are British. Considering that the work is by no means a complete account of electrocardiography, for example the arrhythmias are hardly mentioned as such, the price is high even for these days.

The translation from the Spanish by Dr. Calder is brilliant, and he has succeeded in making most readable this very technical book.

Fluid Balance Handbook for Practitioners. By WILLIAM D. SNIVELY, Jr., M.D., and MICHAEL J. SWEENEY, M.D. Oxford: Blackwell Scientific Publications, 1956. Pp. xix and 326. Figures 27. Price 51*s.*

THERE are many books on body fluids but few are as effectively written for the practitioner and the non-expert as this one. The authors have, to use an Americanism, fallen over backwards to present the intricacies of salt and water metabolism in a comprehensible, easily read form. They have been outstandingly successful and their desire for simplification has not led to too many errors of fact. Thus, although likely to be remembered, it is not entirely acceptable to state that a reduction in electrolyte concentration of the extracellular fluid causes the cells to be filled 'to the bursting point with water'. Some of the more turgid prose in the earlier chapters—'Human extracellular fluid, that salty liquid which bathes our body cells, is truly an ancient fluid. Its primordial ancestor was ocean water of the Paleozoic seas of a third of a billion years ago. It was during this period that the remote ancestors of the human race forsook their marine homeland and ventured ashore to populate the greening continents'—may be unpleasing to English, in contradistinction to American, readers but is readily forgotten and forgiven because the book is so good.

In Their Early Twenties. By PROF. T. FERGUSON and J. CUNNISON. London: Oxford University Press, 1956. Pp. vi and 110. Price 12*s.* 6*d.*

THIS is the continuation of the story of 1,349 Glasgow schoolboys who left school in 1947 at the earliest permitted age, who were studied between 14 and 17 in the book 'The Young

Wage Earner', who have now completed or been rejected for military service, and whose careers during the subsequent two years until 22 is known. Over 500 cases were studied. Approximately 40 per cent. were rejected for military service, and these men came from homes of unskilled manual workers. Although poor physique was such a handicap, by 22 they had settled to their jobs better than the ex-enlisted, and their small crime rate was no worse than that of the ex-soldier, and much better than it had been before 18. The R.A.F. man had had a better personality assessment, physique and background than his Army opposite; a point suggesting more satisfactory screening. And he will get a more skilled job on discharge, and will be more likely to return to his old job than the ex-soldier. He will (provided he comes from this group) escape unemployment more easily than the military man, or the reject. When he is demobilized he is almost four times as likely to join an organized group, games or club. But only 4 per cent. attend evening classes. There is a regrettable tendency for apprenticeships to be given up after return from the Services, and the years there do not encourage men to a life more full of foresight upon discharge. It seems regrettable that of the 20 per cent. who found settling down so difficult, many come from the new estates. Improvement in social conditions seems no guarantee that contentment will follow.

This small volume is to be commended for the light it sheds upon the problems of the young man and his adaptation to a society which, even with full employment elsewhere, allows 6 per cent. unemployment among these men at so impressionable a period of their lives.

Anatomical Techniques. By D. H. Tompsett, B.Sc., Ph.D. Edinburgh: E. & S. Livingstone Ltd., 1956. Pp. xvi and 240. Figures 83. Price 35*s*.

It is fitting that a book concerned with the techniques of production of anatomical specimens should be written by a member of the Royal College of Surgeons of England, which houses the 'John' half of the world's most famous anatomical museum, collected together by the two Hunter brothers. This book gives practical instruction—which can be followed by an intelligent museum technician—on the methods of preparing different types of anatomical specimens. Part I deals with the fixation and injection of dissected specimens together with instruction regarding how and where to mount them. There is a smaller section concerned with the illustration of specimens, incorporating useful advice to the medical artist. The author has made a special study of the production of 'casts', in particular, those of the bronchial tree, heart, blood vessels and brain cavities, and naturally the largest section of the book is devoted to description and instruction in this specialized technique. There is the timely warning that there is a period of trial and error before the tyro can hope to produce the beautiful specimens illustrated in the book. A final brief section on that colourful showpiece, the stained brain slice, is followed by a useful appendix on how and where to obtain the necessary materials.

A book which is a record of personal experience and achievement and which should be read by all interested in the collection and presentation of biological material.

The History of the School of Tropical Medicine in London. By Sir Philip Manson-Bahr, C.M.G., D.S.O., M.D., F.R.C.P. London: H. K. Lewis & Co. Ltd., 1956. Pp. xiv and 329. Figures 30. Price 50*s*.

This, Memoir No. 11 of the London School of Hygiene and Tropical Medicine, is a most enjoyable history, written by a man whose personality enlivens every page. Sir Philip's intimate knowledge and obvious love of the School qualify him before anyone alive to write this book. He recounts how Sir Patrick Manson, against powerful opposition, founded the School with the support of Joseph Chamberlain. He shows how the great discoveries of the early days, which have helped to establish health in the tropics, were achieved in an institution where the biological and clinical sciences were closely linked. He regrets their present separation, and there are no examples better than his to demonstrate their potential cross-fertility. The second half of the book consists of the biographies of the workers at the School, all of whom the author has known personally. There is also an interesting appendix in which are listed the publications of the staff and the diseases encountered in London at the Hospital for Tropical Diseases.

NEW EDITIONS

The Essentials of Modern Surgery, edited by R. M. Handfield-Jones, *M.C.*, M.S., F.R.C.S., and Sir Arthur E. Porritt, K.C.M.G., C.B.E., M.Ch., F.R.C.S., in its fifth edition (E. S. Livingstone Ltd., 75*s*.).—Every medical student needs a textbook sufficiently complete to cover every aspect of surgery and the surgical specialties, sufficiently simple to be clear, yet sufficiently authoritative and up to date to deal with any questions that may arise during clinical work, or that may be asked at examination. 'Handfield-

Jones and Porritt' has long stood high in this category. With more than 1200 pages it is the equivalent of a two-volume work, but it has the advantage of single-volume compactness. Although the book was first published nearly twenty years ago, and has gone through four editions and as many reprints, this is the first occasion on which it has undergone a major revision. The whole work has been brought up to date—indeed, largely rewritten. The illustrations are particularly well chosen. As a general textbook of surgery it can be recommended with confidence to undergraduates and postgraduates alike. But why is the Bunyan bag referred to on page 142 as the Stannard envelope? John Bunyan was the inventor, Stannard the manufacturer.

Sequeira's Diseases of The Skin, in its sixth edition (J. & A. Churchill Ltd., 105*s*.) has been revised by J. T. Ingram, M.D., F.R.C.P., and R. T. Brain, M.D., F.R.C.P., who collaborated with Dr. Sequeira in the preparation of the fifth edition. The chapter on leprosy has been written by Dr. R. G. Cochrane. This new edition maintains all the important attributes of earlier editions—a sound, predominantly clinical review of the subject, in which the authors are at pains to integrate the subject with general medicine. The majority of the 426 illustrations and the 63 coloured plates are admirably reproduced, although perhaps a little more radical pruning would have been helpful. This remains one of the best books on the subject for the general physician—whether in consulting or general practice.

A Companion in Surgical Studies, by Ian Aird, M.Ch., F.R.C.S., in its second edition (E. & S. Livingstone Ltd., 84*s*.) is the notebook of a man who has spent his life in teaching surgery to postgraduate students. He is a hard worker and has an unusual gift for clear writing. The book has earned such a reputation that the man who would contemplate working for a Fellowship in surgery without buying or borrowing a copy would be looked on by his fellows as almost certifiable. The new edition, which contains much new material, will be sure of a warm welcome.

The Diseases of Occupations, by Donald Hunter, M.D., F.R.C.P., in its second edition (English Universities Press Ltd., 105*s*.) appears only two years after the first edition. This in itself is striking tribute to its quality. In this edition new sections have been added on thallium poisoning, on iron and steel foundries and on the hazards of work in sewers, and the sections on poisoning by cadmium, manganese and vanadium have been brought up to date. There are many other textbooks on industrial diseases, but there is none other which has the historic sweep, the clinical approach or the terseness of style of this one. 'Hunter on Occupational Diseases' will long remain a classic. The illustrations (there are over 400 of them) are among the outstanding features of the book. It is all the more the pity therefore that the standard of reproduction is not equal to the skill shown in their selection.

Blood Transfusion in Clinical Medicine, by P. L. Mollison, M.D., M.R.C.P., in its second edition (Blackwell Scientific Publications, 45*s*.) has been enlarged by 100 pages to include the principal advances in transfusion practice and technique of the past five years. Outstanding among many new sections are: methods for the determination of red cell survival and red cell mass employing radioactive chromium, the prolonged storage of red cells in the frozen state, transfusion of the injured patient, and hæmolytic disease of the newborn resulting from mother-child ABO incompatibility. Clinicians and pathologists will find that this book contains a clear, authoritative and up-to-date account of all aspects of blood transfusion, and it can be recommended as the best available on this subject.

Clinical Pathology: Applications and Interpretation, by Benjamin B. Wells, M.D., PH.D., in its second edition (W. B. Saunders Co., 59*s*. 6*d*.,) represents an extensive review of the original volume which appeared in 1950. The general arrangement of each chapter has been preserved, but in some instances sections have been enlarged and rearranged: for example, consideration of viral and rickettsial diseases now appears at great length and in a more prominent position. New material is also incorporated, as for example on hypersplenism, radioiodine, electrolytes and water balance, and the significance of 17-ketosteroids. The final chapter, which in the original volume was an appendix dealing with laboratory aids in symptom diagnosis, e.g. sputum examination, now contains a more extensive reference to such laboratory procedures as can be readily carried out in the 'ward laboratory'. Not the least valuable feature of this excellent book is what A. H. Sanford in the preface calls the 'philosophy of the author in his introductory considerations'. This is the feature which makes the book particularly suitable to the clinical unit where there is always a need for helpful guidance on the application and interpretation of laboratory methods.

The contents of the May issue, which will contain a symposium on 'Diseases of the Eye' will be found on page A108 at the end of the advertisement section.

Notes and Preparations see page 515.
Fifty Years Ago see page 519.
Motoring Notes see page A87.
Travel Notes see page A91.

'MEPAVLON', I.C.I.'s new tranquilliser, is distinguished by its ability to relieve both mental and muscular tension without dulling consciousness. It has proved to be particularly suitable for calming the nervous patient troubled with anxiety, restlessness and irritability. In such cases, 'Mepavlon' stabilises the emotions, relaxes tension and relieves nervous insomnia by inducing natural sleep. No less important: its toxicity is low, it is well tolerated, and side effects are rare.

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NOTES AND PREPARATIONS

NEW PREPARATIONS

'DELTALGYCORTRIL' tablets each contain 0.5 mg. of 'deltacortril' brand prednisolone and 300 mg. of aspirin, and are for use in 'controlling symptoms in less severe rheumatic and arthritic conditions'. Issued in bottles of 100 tablets. (Pfizer Ltd., 137-139 Sandgate Road, Folkestone, Kent.)

'LOCAN' pessaries each contain amethocaine, 10 mg.; amylocaine, 5 mg.; solution of benzalkonium chloride B.P.C., 0.02 ml.; lactic acid, 30 mg., and lactose, 250 mg., and are intended for the treatment of trichomonal, monilial and non-specific vaginitis and cervicitis. They are said to 'provide an immediate soothing action with rapid control of infection and the restoration and maintenance of the normal vaginal physiology' and to incorporate 'a new type of base which rapidly melts and diffuses, but does not leak, stain or soil clothing'. Issued in boxes of 12 and 72 pessaries. (Allied Laboratories Ltd., 140 Park Lane, London, W.1.)

'NITENSAR' tablets each contain quinalbarbitone sodium, 12.2 mg.; pentobarbitone sodium, 12.2 mg.; butobarbitone sodium, 4 mg.; phenobarbitone, 4 mg.; and reserpine 0.1 mg., and are indicated 'whenever gentle tranquillization is considered beneficial to the patient'. They are said to act within 20 minutes, to produce 'smooth, consecutive deepening of the calming effect'. Issued in bottles of 50, 100 and 1000 tablets. (Armour Laboratories, Hampden Park, Eastbourne, Sussex.)

'PENAVLON' V tablets each contain the equivalent of 120 mg. (free acid) of penicillin V (phenoxymethylpenicillin), equivalent to 200,000 units of penicillin G. Issued in tubes of 15 and bottles of 100 and 500 scored tablets. (Imperial Chemical Industries Ltd., Pharmaceuticals Division, Fulshaw Hall, Wilmslow, Cheshire.)

PHARMACEUTICAL NOTES

CAMDEN CHEMICAL CO. LTD. announce that they are now marketing 'cafron' brand benactyzine hydrochloride in tablets of 1 mg. (sugar-coated). Issued in bottles of 100 and 1000. (61 Gray's Inn Road, London, W.C.1.)

PFIZER LTD. announce that their nasal decongestant 'tyzanol' is now available in a pædiatric concentration for use in infants and in young children under six years of age. Issued in bottles containing 15 ml. of 0.05% tetrahydrozoline hydrochloride, with calibrated droppers. (137-139 Sandgate Road, Folkestone, Kent.)

ROUSSEL LABORATORIES LTD. announce that 'hydrocortisyl' skin spray has been added to their range of hydrocortisone preparations, in the form of a 'pressurized ½% solution', supplied in bottles of 100 ml. (847 Harrow Road, London, N.W. 10.)

COURSES AND CONFERENCES

THE *Seventh International Cancer Congress* sponsored by the International Union Against Cancer will be held in London from July 6 to 12, 1958, under the presidency of Sir Stanford Cade. Full details and enrolment forms may be obtained from the Secretary, Seventh International Cancer Congress, 45 Lincoln's Inn Fields, London, W.C.2.

Chest Diseases and the Family Doctor will be the subject at a weekend intensive postgraduate course for medical practitioners, to be held in Norwich on April 13 and 14, 1957. Details may be obtained from the Tuberculosis Educational Institute, Tavistock House North, Tavistock Square, London, W.C.1.

The Child and His Home will be the subject for discussion at a summer school organized by the British Social Biology Council, to be held at the Cité Universitaire, Aix-en-Provence, France, from August 24 to September 8, 1957. Further information may be obtained from the British Social Biology Council, Tavistock House South, Tavistock Square, London, W.C.1.

FILM NEWS

The Diabetic Diet (16 mm., commentary; running time 15 minutes) is intended as an aid to the instruction of diabetics and those who care for them. Produced by Eothen Films in cooperation with the Medical Advisory Committee of the British Diabetic Association and written and directed by Philip Sattin. On free loan from the Gaumont British Film Library, Aintree Road, Perivale, Greenford, Middlesex.

RADIOACTIVE ISOTOPES IN MEDICINE

A COURSE on *Radioactive Isotopes in Medicine* will be held in Sheffield and London from September 15 to 28, 1957, for overseas qualified medical practitioners who are proficient in English. Further details may be obtained from the local representative of the British Council or, for those resident in the United Kingdom, from the Director, Courses Department, The British Council, 65 Davies Street, London, W.1.

MEDICAL RESEARCH IN SCOTLAND

THE Scottish Hospital Endowments Research Trust, which administers a sum in excess of £2 million, formerly part of the funds of Scottish voluntary hospitals, has just published its first annual report, covering the period January 12, 1954, to July 31, 1955. Its funds give it an annual income of the order of £90,000, but experience shows already that this may be less than adequate if all promising projects are to be assisted. The trustees are empowered to hold and administer further sums and, in a letter accompanying the annual report, Sir John Maxwell Erskine, the chairman of the Trust, expresses 'the hope that this will be kept in view by Scottish people who have a long-standing tradition of making donations and bequests for scientific purposes in this field'. The address of the Trust is 12 Hope Street, Charlotte Square, Edinburgh, 2.

THE INSTITUTE OF PSYCHIATRY

THE annual report of the Institute of Psychiatry of the University of London for the year ended July 31, 1956, contains details of an examination of the records of 11,000 patients admitted during 1947-49 to the two largest observation units in London and to certain mental hospitals serving the metropolitan area. Of the 9000 patients admitted to the observation units, just over a quarter recovered quickly from a short-lived disturbance and were able to return home in two or three weeks. Seven per cent. of those admitted died in the observation units. From the first admission rates it is calculated that, out of every thousand babies born, 53 will be admitted at least once in their life to a mental hospital; 10 of these will suffer from schizophrenia, 11 from manic-depressive and involutional psychoses, and 24 from psychoses of old age.

The investigation also showed that single persons are more likely to enter mental hospitals than married persons, and once in they are less likely to reach the point at which they can be discharged. Thus, in the group of men aged between 30 and 49, the number of first admissions per million was 1,455 (±196) for single men and 299 (±38) for married men; the corresponding figures for women were 1,262 (±173) and 536 (±52). Of the schizophrenic patients admitted, 60% were discharged within a year. During the follow-up period of 3½ years, a third of the schizophrenic patients were readmitted at least once. 'In spite of recent advances in treatment, there are still many patients who have had to spend years, and perhaps the rest of their lives, in a mental hospital'. Of the patients in such hospitals on any given day, 85% have been there at least one year, 77% for two years, 64% for five years, and 48% for ten years.

CHIROPODY FOR OLD PEOPLE

OF the 208 applications for grants received by the National Corporation for the Care of Old People during the year ended September 30, 1956, 193 were for assistance for chiropody schemes for old people. Many more requests for help for such schemes were received, but they had to be refused because of the limitation of funds allocated for this purpose. Attention is drawn to the fact that the Ministry of Health has recognized as competent to operate in the National Health Service only chiropodists whose standard of training reaches an approved level. This excludes many who practise chiropody after receiving their training by correspondence course. A plea is made in the annual report of the Corporation for reconsideration of this question of standards. In the opinion of the Corporation, 'this question of standards—in spite of the many inherent difficulties—and of numbers is one the Governors believe is even more important than that of finance'.

NATIONAL LIFE TABLES

THE 'Life Tables' volume of the 'Registrar General's Decennial Supplement, England & Wales. 1951' (H.M. Stationery Office, price 3s.) show that the expectation of life for a boy at birth has increased by nearly 15 years in the past forty years; for a girl the increase is more than 16 years. In 1910-12, 120 of every 1000 boys born and 98 of every 1000 girls born died before reaching their first birthday; the corresponding figures for 1950-52 were 33 boys and 25 girls. In adult life, women are still faring better than men. At age 60, for instance, the expectation for men on 1950-52 mortality is about 14¾ years, an increase of only ¾ year on the figure twenty years earlier, whereas for women it is now 18 years, an increase of 1½ years in this period. Persons living in England have a higher expectation of life than those living in Scotland or Wales. There are considerable variations between different parts of the country. In the Merseyside conurbation, for example, the mortality for men was 21% above the national average, whilst in the Eastern region (mainly rural) the mortality for men was 14% below the national average.

MEMORIAL TO SIR ALEXANDER FLEMING

THE townspeople of Darvel, Ayrshire, have aised £2,500 to provide a memorial to Sirr Alexander Fleming, who was born there in

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1. *Wis. med. J.* (1954) 53:322.
2. *Amer. J. Obstet. Gynec.* (1954) 9:201.
3. *J. Indiana med. Ass.* (1954) 47:989
4. *J. Clin. Endocr.* (1954) 14:372.

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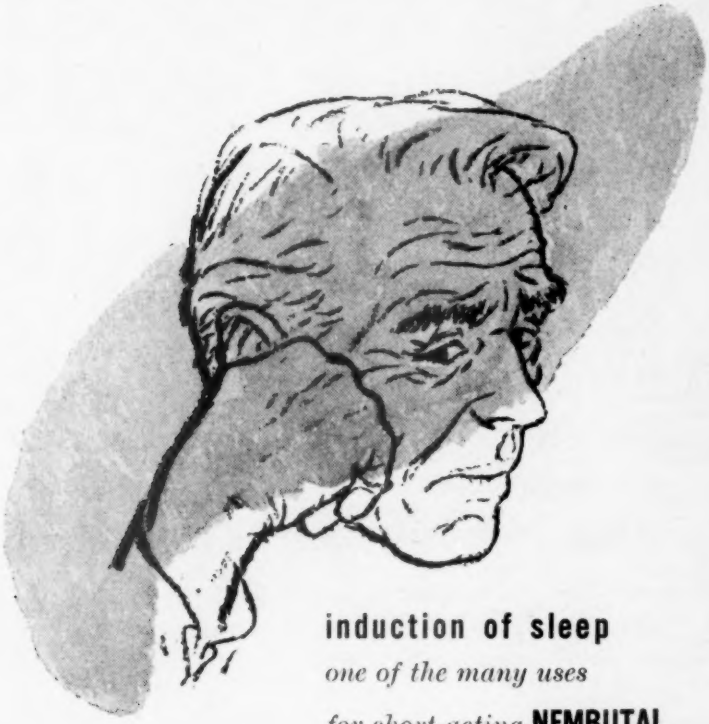

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NEMBUTAL

1881. To this sum five British manufacturers of penicillin have added the sum of £2,100. Plans for the memorial include the provision of a clinic or a research scholarship, and the erection of a notice at the entrance to the town marking it as Sir Alexander Fleming's birthplace.

THE WELFARE BOOMERANG ?

THE following is an excerpt from the annual report for 1956 of Dr. John Maddison, the medical officer of health for Twickenham. 'In the infant welfare clinics we have been noticing that a number of younger mothers seem to complain more of fatigue than their mothers used to do. These younger women are those with one or two young children; they usually come from good homes where the standards are high. I wonder if the struggle for the maintenance of high standards of health and well-being; the possession of a good home and furniture, the keeping up of appearances with the neighbours; the maintenance of a high standard of infant and child welfare; the pressure on all sides from the welfare services, women's magazines, and other sources of information and teaching, whether all these tend to exhaust our mothers too much. Forty years ago, I fancy our mothers weren't so well informed; so I wonder if the fatigue is due to the pressure of modern life, or do our present-day standards demand too much? We must not let our quest for excellence be so strong and enthusiastic as to be inimical to the welfare of those for whom it is intended'.

MEAT CONSUMPTION

NEW Zealanders are the biggest meat eaters in the world, according to some recently published figures for world consumption of meat. In 1955, they ate an average of 216 pounds (98 kg.) per head. Australians came next, with an average consumption per head of 211 pounds (96 kg.). The comparable figure for the United Kingdom is 128 pounds (58 kg.), compared with an average of 101 pounds (46 kg.) for the five-year period after the War. The United States and Canada ranked fifth and sixth, their consumption being 161 pounds (73 kg.) and 146 pounds (66 kg.) respectively.

CLEANSING OYSTERS

SINCE it was established in 1934, the Brightlingsea Purification Station has treated 46 million oysters, valued at over £700,000 (at 1956 prices) without a single case of illness attributed to their consumption. This excellent record has been maintained in spite of topographical and bacteriological evidence that the oysters from this locality may be heavily polluted. In reporting these figures, P. C. Wood, of the Ministry of Agriculture, Fisheries, and Food Fisheries Laboratory, Burnham-on-Crouch (*Publ. Hlth (Lond.)*, 1957, **70**, 92) gives details of recent changes in the methods of treating oysters which have resulted in considerable financial saving. For long it was considered that the ability of oysters to cleanse themselves was reduced at low water temperatures, and a minimum water temperature of 54° F. (12.2° C.) was adopted at Brightlingsea. Subsequent investigations have shown that a temperature of 41° F. (5° C.) is adequate. This means that the treatment water has now to be warmed for only a few weeks, instead of regularly each year from September to May.

PROFESSIONAL FOOTBALLERS' I.Q.

PROFESSIONAL footballers are more intelligent than the people who watch them play, according to French psychologists as a result of an investigation they have carried out on 108 professional footballers. The investigation was made at the request of the French Football Federation which is trying to find out how to place footballers when they become too old to play or have to retire because of injuries. The investigation showed that the average footballer's intelligence quotient was noticeably higher than that of spectators, the I.Q. of the latter being based upon figures for the 'average Frenchman'.

COMMUNICATION THROUGH ART

'Communication through Art' is an exhibition of pictures executed as occupational therapy by patients in mental hospitals. Its purpose is to provide psychiatrists who have not previously made use of painting with an opportunity of assessing its possible worth in their own relationships with patients. It is available for showing at any mental hospital. Superintendents of such hospitals, who are interested in the matter, can obtain full details from William R. Warner & Co. Ltd., Power Road, London, W.4, who will be pleased to make arrangements for the transportation and setting up of the pictures.

PUBLICATIONS

The Treatment of High Blood Pressure, by F. H. Smirk, M.D., F.R.C.P., is the George Alexander Gibson Lecture delivered before the Royal College of Physicians of Edinburgh last year. Although the lecturer reaches the somewhat depressing conclusion that 'the skill and time expenditure required to dodge side-effects makes it evident that the drugs we have available at present are far from ideal', his account of the

ganglion-blocking drugs will be read with profit by all clinicians. (The Royal College of Physicians of Edinburgh, price 3*s*. 6*d*.)

Looking after Old People at Home, by Doreen Norton, S.R.N., is an excellent practical guide to the subject, written for relatives and friends who have to look after old people. Practitioners are strongly advised to obtain a copy, not only for their own benefit, but also so that they can recommend it in suitable cases in their practices. (The National Council of Social Service, price 2*s*. 6*d*., or 2*s*. 10*d*. post free.)

You and Your Baby, which is described as a '*Family Doctor* Special', is an admirable guide to the subject written by a host of experts, including Professor J. C. McClure Browne. Professor Dugald Baird, Professor R. S. Illingworth, Dr. A. P. Norman and Dr. Dermod MacCarthy. It is not on sale in the ordinary way and is being distributed only by doctors to their patients. Bulk prices can be quoted to doctors only, on application to *Family Doctor*, B.M.A. House, Tavistock Square, London, W.C.1.

Dental Health, edited by Professor H. H. Stones, M.D., M.D.S., F.D.S. R.C.S., is an excellent book, meant primarily for teachers, parents and other 'educated laymen'. There is a full glossary, including a little Greek. More than sixty photographs and diagrams, mostly in colour, add to the clear descriptions dealing with the anatomy and development of teeth, common dental diseases and their prevention by diet and sensible rules for the nursery and schoolroom. One small criticism: a child with mouth-breathing (p. 67) should be seen first by the family doctor, not referred direct to an E.N.T. specialist. (The Dental Health Board of the United Kingdom, price 10*s*. 6*d*.)

The Christchurch Hospital Medical Manual, edited by C. T. Hand Newton, D.S.O., M.D., F.R.A.C.P., F.R.C.S.ED., in its fourth edition is essentially designed for the use of students and house officers of the Christchurch Hospital, in order to obtain a measure of uniformity in administrative clinical routine. For this purpose sections are contributed by the pathological, x-ray, dietary and other departments. Apart from its purely local features, the general principles of which might well apply in any large hospital, the information concerning pathological investigations and their interpretation, special diets and many other details is clear and accurate and would be found universally valuable. It is a good little book of its kind and has been thoughtfully and carefully prepared. (N. M. Peryer Ltd., and Lloyd Luke, price 27*s*.)

OFFICIAL PUBLICATIONS

Health Services in Britain is one of a series of pamphlets produced by the Central Office of Information for the Overseas Information Service. It provides a factual account of the subject which will be read with interest by many in the United Kingdom as well as abroad. Needless to say, it paints as rosy a picture as possible of the National Health Service, but there has been a laudable attempt to maintain a reasonable degree of impartiality. (H.M. Stationery Office, price 3*s*.)

Health Education (Ministry of Education pamphlet 31) is described as 'a handbook of suggestions for the consideration of teachers and others concerned in the health and education of children and young people'. Fortunately the contents are not in the same tradition as the photograph which 'graces' the cover, and it is a pamphlet which can be unreservedly commended to all concerned with this important subject. (H.M. Stationery Office, price 4*s*.)

The Medical Service of the Royal Navy

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Full particulars from the Admiralty Medical Department, Queen Anne's Mansions, St. James's Park, London, S.W.1.

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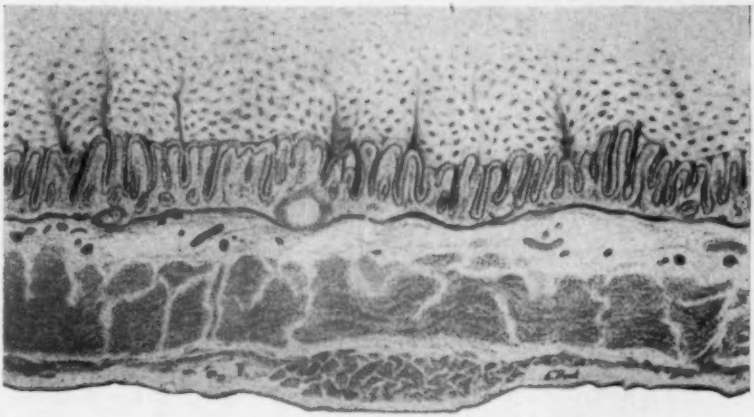

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THE PRACTITIONER

Fifty Years Ago

'Man is a machine into which are put what we call food
and produce what we call thought'.—R. G. Ingersoll: *The Gods.*

APRIL 1907

'THE fusion of the medical societies of London into one strong body that should be able, like the French Académie de Médecine, to speak with authority in the name of the profession on scientific questions, has often been advocated by *The Practitioner*'. The Editor, therefore, hails with satisfaction 'the amalgamation, partial as it is, that has been effected. It is not indeed the organization of which we have dreamed, but it may perhaps be looked upon as an intermediate stage in its development. . . . While rejoicing that the first step to a union of our scientific forces has been taken, we cannot help regretting that it has been decided to call the new body the Royal Society of Medicine. It is almost a colourable imitation of the title of the greatest and most ancient of our scientific associations, and it is to be feared that it will lend itself to misapprehension and even misuse. The public cannot be expected to discriminate very exactly between one Royal Society and another, and unfortunately it is not altogether inconceivable that some members might not take the trouble to dispel the confusion'.

'Philosophers have had much difficulty in providing a satisfactory definition of man [according to "Notes by the Way"]. Plato's "biped without feathers" failed to stand a practical test. . . . There is room, therefore, for a new definition of man, and we venture to propose "an animal deluded by advertisement" as meeting the requirements of the case. Man changes in everything else; he has rid himself of many superstitions, but he is still as much the prey of the advertiser as he was when he allowed himself to be gulled by the records of cures inscribed on the walls of the temples of Asklepios in ancient Greece. Many of these are exactly in the style of the infallible nostrums which are pillars of support for our free and independent press of the present day. And wherever we strike the trail of the advertiser through the ages, it is always the same kind of thing'.

The first of the 'Original Communications' entitled 'The Treatment of Post-Partum Hæmorrhage' introduces a note of novelty, for its author, G. E. Herman, F.R.C.P., F.R.C.S., Consulting Obstetric Physician to the London Hospital, had been asked by the Editor 'to criticise three articles on the subject, which appeared in the issues of August and November 1906, and February 1907'. George Ernest Herman was appointed Obstetric Physician to 'The London' in 1883. He was a brilliant operator and a fine clinical teacher. Entertained to dinner by his former Residents in July 1903 upon being elected consulting obstetric physician, he

George Ernest Herman, F.R.C.P., F.R.C.S.
(1849-1914)

began his speech: 'As has been well said, there is more joy over one senior that resigneth, than over ninety and nine just appointed persons'.

John Cowan, M.D., Physician to the Royal Infirmary, Glasgow, discusses 'The Myogenic Theory' of the cardiac action; Frederick Langmead, M.D., M.R.C.P., Physician to Outpatients, Paddington Green Children's Hospital, takes as his subject 'The Relationship between Simple Posterior Basic Meningitis and

Cerebro-spinal Fever'; and A. F. Hertz, M.B., M.R.C.P., Demonstrator of Physiology and Pharmacology at Guy's Hospital Medical School, presents 'Notes from Germany on the Value of Röntgen Rays in Medical Diagnosis'.

'Carlyle somewhere says that, by careful search, it might be possible to discover the greatest fool extant at any given time. It might be difficult to say who was the greatest quack that ever lived, but if matchless impudence were to be accepted as the test, a well-founded claim might be made on behalf of James Graham, the high priest of the Temple of Health of which the Goddess was Lady Hamilton. . . . Thither at one time flocked the fashionable society of London, to listen to what many of them must have known to be quackery of the vilest kind, and to be treated by methods openly intended for the stimulation of lust rather than for the healing of disease'.

A number of popular books are reviewed this month. Walter E. Dixon's 'A Manual of Pharmacology' is highly commended 'to all practitioners of medicine, who take an interest in the action of drugs'. Of 'Recent Advances in Physiology and Bio-Chemistry', edited by Leonard Hill, the reviewer writes: 'This excellent work, which is admirably produced, may be recommended to all medical men, who desire to acquaint themselves with the latest views upon the subjects'. 'A Treatise on Surgery' by George Ryerson Fowler 'seems to us somewhat unequal, and we may perhaps be allowed to enter a protest against its excessive weight, which is, we believe, due to the free use of bismuth in the preparation of the paper'.

'Practical Notes' quote from an article on 'Nocturnal Enuresis' in *Gazette Médicale de Paris*:—'The most frequent causes of this bad habit are hyperacidity of the urine and abnormally deep sleep. When the former is proved to be present, it is usually enough to give alkaline remedies in order to obtain a cure. When the wetting occurs as a consequence of too deep a sleep, the best measure to adopt is systematic awakening of the child. In order to carry out this method thoroughly in the case of inveteracy, and to force the child to get accustomed to waking up at the critical moment, the following procedure has been tried with success: The child lies upon a mattress composed of two layers of metallic tissue separated by a dry cloth. . . . Each of these layers is connected by a wire to the working part of a loud electric bell placed above the bed. As soon as the first drop of urine has damped the cloth, and so made contact, the bell rings furiously, and wakens the sleeper. By reflex inhibition, the action of the bladder is stayed. From two to five repetitions of this experience are said to be sufficient for a radical cure'.

W. R. B.

1907 — Fifty years of service to the medical profession — 1957

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MOTORING NOTES

Selecting a New Car

By ROBERT NEIL

THE recent announcement of the new Vauxhall Victor has given fresh impetus to the inevitable discussions about the ideal car for a practitioner. An increasing number of doctors throughout the country must be finding that the ever-rising overhead costs in their practices indicate that it would be wise to run a smaller and more economical car than has been the general rule. Because of the well-deserved reputation for economy enjoyed by all Vauxhall models the new Victor has been hailed as the solution to many motorists' problems. The makers of this new car will, I hope, forgive me if I point out to readers that when buying such an important and expensive item of equipment as a motor car it is better not to be egged on by a sudden burst of enthusiasm, but to study the pros and cons with extreme *sang froid*.

THE CAR FOR THE JOB

What I think many motorists forget, and perhaps practitioners more than others, is the particular purposes for which their car is most important. Few would sympathize with a commercial traveller who used his firm's money to buy a car which was perfect for the occasional week-end trip, but was quite unsuitable for the business for which it was intended. It is fatally easy for the driver to be so impressed by the performance, or the handiness of the controls, to forget such points as visibility from the rear seats—even though his child might suffer from car sickness—or the dimensions of the luggage boot. It is essential to go through any prospective new car's specification with a most analytical and suspicious mind. I feel that many doctors who use their cars day after day will agree with me that one of the greatest irritations is having to put their car off the road every now and then to have essential greasing and servicing carried out. It is therefore necessary before deciding on an individual car to check by means of the instruction book how many, and at what intervals, points require attention with the grease gun. When such cars as Bentley, Rolls-Royce and Rover are run this is no problem, as the use of centralized chassis lubrication systems or the use of rubber bearings and sealed oil-packed bearings, increases considerably the intervals between servicing.

One point which some motorists seem to forget when choosing a new car is the number of doors which will best suit their purpose. If the rear seat is only occupied occasionally it is worth while considering the purchase of a two-door saloon, which has the other advantages that the driver's door will be wider than normal, making entry or exit easier, whilst a motorist with very young children is spared the worry of a rear door opening unexpectedly. The four-door saloon however, is probably better if the rear seat is used much, as the disadvantage of the two-door body lies in the necessity for either the driver or the front passenger to get out to free the way for a passenger from the rear compartment. I agree that this may seem a very simple point when one reads it, but there must be many motorists who would agree that they have often forgotten it—to their sorrow.

On more technical points there is probably even more confused thinking. Merely because a friend, of whose driving style and habits they know nothing, has had excellent service from a particular car, many motorists follow his example blindly only to find disillusionment. The friend might easily be a driver who enjoys driving and gear changing, and had selected a high-geared car with a four-speed gearbox. This would be unsuitable for our hypothetical purchaser, whose real wants would best be filled by a smooth effortless car with a three-speed gearbox, which would give him labour-free driving.

THE VAUXHALL VICTOR

Bearing these thoughts in mind it is of special interest to study the specification of the new Vauxhall Victor (fig. 1, 2). As this car is obviously intended for very large-scale production, which means that it must please a wide section of the motoring public, it is perforce a compromise, but a remarkably successful one. For many years now all Vauxhall models have had a justified reputation for economy, to such an extent that there is no car of equivalent performance, size and price which can equal their fuel consumption figures, and there is every reason to believe that this new model will surpass its bigger sister cars. At the moment of writing I have not had the opportunity of carrying out a test, but it can be accepted that the fuel consumption obtained by owners will vary between 28 and 35 m.p.g.

One of the conveniences of the modern car which many motorists have come to regard as an essential is the heating and demisting system. It is of interest that the type fitted to the Vauxhall is most efficient, and if the trouble is taken by the owner to blank off the radiator appropriately during the winter months—so that working temperature will be quickly

reached—this is, in itself, a great boon to practitioners, who might be called out in the middle of the night.

As a large proportion of the Vauxhall Victor's power is produced at relatively low engine speeds the gears do not require to be used so often as on many other cars; this undoubtedly reduces the effort of driving. Bottom gear need only be used for getting away from rest, whilst second gear can be used down to any speed other than a full stop. This new car is the first car built in Europe to use a panoramic windscreen, and the forward vision is remarkably good, providing a wide angle without the interference of windscreen pillars. This benefit carries with it a slight disadvantage. As it is a relatively small car the bringing back of the windscreen sides causes a reduction in the effective door space; about a quarter of the front

FIG. 1.—The new Vauxhall Victor.

FIG. 2.—Interior of the new Vauxhall Victor.

door width is made ineffective by the intrusion of the windscreen (fig. 2). This, however, is a point which will probably be forgotten after one has driven the car for a few days.

TOO MUCH CHROMIUM

The point on which the Victor can be justifiably criticized is in the lavish use of chromium as mere ornamentation. The constant worry of keeping the plating in a presentable condition is one that the average busy motorist would be happier without. The rectangular lines of the rear wings and the luggage boot give two benefits. The horizontal top line of the rear wings allows them to be seen easily by the driver, with the result that reversing can be a very accurate manœuvre, whilst the box-like angularity makes the luggage boot remarkably roomy. For styling reasons the bumpers on the new Vauxhall are not separate from the bodywork (fig. 1) and, although this improves the appearance, it may have the disadvantage that minor bumps—as are likely to be received in a car park—could be transmitted to the bodywork itself.

As the Vauxhall Victor is being offered at a low price, and combines a 75 m.p.h. performance with economical running, it is likely to become a very popular car on British roads, as well as elsewhere.

PARKING PROBLEMS

Readers who live or work in London will be well aware of the parking problem, which faces both the Government and the everyday motorist. It is unfortunate that the schemes of the Minister of Transport seem to be based entirely upon restriction and obstruction, rather than on a single common-sense approach to the problem. Too many motorists, in my opinion, in their estimable attempts to be good citizens, sit down under the most inept and shortsighted of policies. It is entirely the responsibility of the Minister of Transport to provide the means for the motor vehicle to continue to contribute to the business and professional life of the country, and merely to say that motor cars will not be allowed in London is a childish evasion of the problem. The Committee on Parking in the Inner Area of London has suggested that in the future only 50 per cent. of the cars entering London in normal times should be allowed. Many readers will recall the conditions which ruled during the railway strike of 1955. The sudden increase of motor cars entering London caused complete confusion for a few days, but realistic action by the police produced a flow of traffic considerably better than existed with less cars before the strike. This was entirely due to the fact that it was realized that an emergency existed, and the police urged the traffic in to moving as fast as is common in Paris.

The lack of forethought demonstrated by the Government's predecessors is no excuse for following their example. The Minister of Transport should institute at once a vigorous policy for speeding up traffic as such, and to provide vast extra parking spaces around the perimeter of Inner London—not, as has been suggested, at Underground Stations about 10 to 15 miles from London.

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TRAVEL NOTES

Taking the Family Abroad

By PENELOPE TURING

JUDGING by the letters which I have received, a large number of readers are considering the question of a family holiday on the Continent and would like details on the pros and cons of different countries and districts. Here therefore are a few facts and suggestions which I hope may be of some use.

In general the basic principles seem to me to be these: for children up to the age of, let us say, 14, sea and a good bathing beach are almost essential; for parents reasonably comfortable accommodation, good food and a place where the children are welcome are vital to the success of any holiday; and finally the shorter the journey the better, both from the financial angle and for the sake of the family's nerves.

THE BRITTANY COAST

Nearly all these qualifications can be found on the coasts of Brittany. Here there are wonderful beaches with wide, flat sands and some of the safest bathing to be found anywhere. I was talking about this to a man who knows France better than many of its natives, and speaking from experience with his own child he put Brittany before anywhere else. The fishing villages (fig. 1) and small seaside resorts west of St. Malo are ideal for a young family, and the average one-star hotels can be relied on for cleanliness and excellent cooking. They are bare, of course, often simple in the extreme, but children are always welcomed and often can do no wrong in the eyes of the proprietors, which certainly helps the holiday atmosphere. St. Briac, just west of St. Malo and Dinard, is a charming example of

FIG. 1.—The fishing fleet at Concarneau, Brittany.

these little towns with lovely sands and a succession of fascinating bays, each with its rock pools.

The journey is not, perhaps, very short, but it is straightforward. You take the night boat from Southampton to St. Malo (about 10 hours) and from there a special coach service runs to

FIG. 2.—Morgat on the coast of Brittany.

the more important centres along the north coast: St. Cast, Erquy, Le Val André, St. Brieuc, Trébeurden, Trégastel and Perros-Guirec. Alternatively you can fly to Dinard.

On the west coast there are more attractive places: Morgat (fig. 2), for example, and Bénodet where the Hotel à l'Ancre de Marine offers really first-class cooking.

My own first trip abroad at the age of four was to another and far more sophisticated French resort, Le Touquet. The bathing was not, I think, very safe, for coastguardmen were on duty to rescue over-adventurous swimmers. I have not been there since, but a friend tells me that it is now much more of a family centre with special games and P.T. organized for children on parts of the beach.

THE BELGIAN COASTAL TOWNS

The Belgian coastal towns are another happy hunting ground for children, and the journey is shorter than that to Brittany. The day crossing from Dover takes 3½ hours to Ostend, from which an electric tram service runs all along the

coast. There are 40 miles of unbroken sands, and the seaside towns vary to suit most tastes. Personally I would prefer to get away from the bustle and day trippers of Ostend to, perhaps, Knocke with its Siamese twin, Le Zoute. These are the easternmost resorts close to the Dutch border, and one can easily make a day trip across to Flushing and on to Middelburg. Knocke has attractions for all ages: a casino which is the social centre, several golf courses, numberless tennis courts, and so on.

As a contrast one of the quietest places along this coast is Brédene, only ten minutes by tram from Ostend quay. Here there is a good sand beach backed by dunes, a few hotels and pensions and a golf course not far away; a typical small family resort. Just a little farther east of this is another small place, Le Coq-sur-Mer. This is a cheerful little open-air village where there is only a short promenade and every villa has its garden, for Le Coq considers flowers its hallmark. West of Ostend, Middelkerke is a good place for children, with a 6-mile promenade and fine sands.

Another advantage of this stretch of coast is that several of the most beautiful and interesting cities of Belgium are within easy reach by day trip. Bruges which somehow never loses its fascination however many trippers crowd its streets or walk through the timeless peace of the Béguinage, Ghent, and even Brussels. From Knocke Brussels is only one-and-a-half hours by train, and a day there makes an ideal contrast to the seaside, including perhaps a superb and expensive lunch at one of the first-class restaurants among the old guild houses of the Grand' Place.

ITALIAN SUNSHINE

By this time someone has probably remarked that sunshine is almost as important as sea, and Belgium and Brittany are too far north to guarantee it. For warmth and sunshine Italy is of course one of the best choices, and with young children I would advise flying out. The boat and train journeys take 27 hours or more, which is a long trip even for an adult, whereas by air the time is reduced to 3 or 4 hours, plus of course journeys to and from the airport.

At the western end of the Italian Riviera are San Remo (fig. 3) and Alassio; farther south and just north of Pisa is Viareggio, and on the Adriatic coast a whole string of places south of Venice; Rimini, Riccione, Cattolica and others. All these have wonderful beaches which are packed with people at the height of the season, a good range of accommodation and as much colour and warmth as anyone could wish; in July and August the average 24-hour temperature is seldom below 70°F.

HOLIDAY CAMPS

Where economy is a vital factor and sea and sunshine outweigh the charms of luxury, a holiday camp is worth consideration. Cooks have their St. Aygulf Holiday Village on the French Riviera between St. Raphael and St. Tropez where you can stay in individual chalets (with cold running water), and cafeteria meals are provided in a central clubhouse. Many people find this solves the problem of an inexpensive family holiday, for the charges are very modest.

FIG. 3.—The Beach at San Remo.

There are, of course, literally thousands of other places on the Mediterranean shores and elsewhere which are ideal for children and grown-ups alike: the Spanish Costa Brava and Costa del Sol, the coast of Portugal, and so on. I myself would not recommend taking very small children, certainly not those under five years old, to the out-of-the-way places because of local difficulties such as shortage of fresh milk, or drinking water problems, which may crop up. But for older ones with a taste for adventure there is really no limit to the range of possible holidays.

One thing, however, has to be borne in mind: school holiday times are much the same all over Europe and they coincide with the peak period for adult tourists also. This means that bookings are heaviest and prices highest at that time of year, so that it is important to make reservations at hotels, on planes and for ships' berths as early as possible.

From April 1 to October 31 there are daily flights to Dinard (1 hour, 55 minutes) for a return fare of £15 3s.; from the beginning of June to mid-September mid-week 15-day excursion returns cost £12 10s. By boat the return fares Southampton-St. Malo are £10 11s. 3d. 1st class, £7 13s. 9d. 2nd class. For Belgium the boat crossing Dover-Ostend is £5 2s. return 1st class; £3 18s. 2nd class. From May till September there are direct flights to Venice on Thursdays and Saturdays (2 hours, 55 minutes) for £41 5s. return; £33 by night flight. To Nice (for San Remo) the flight takes 4 hours, 25 minutes, return fare £37 15s. A ten days' inclusive holiday at Cook's Holiday Village costs £24 15s.; children of 10-15 and 4-10 years £22 15s. and £19 15s., respectively.

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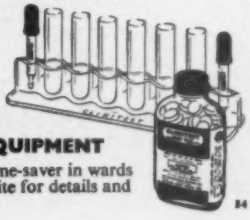

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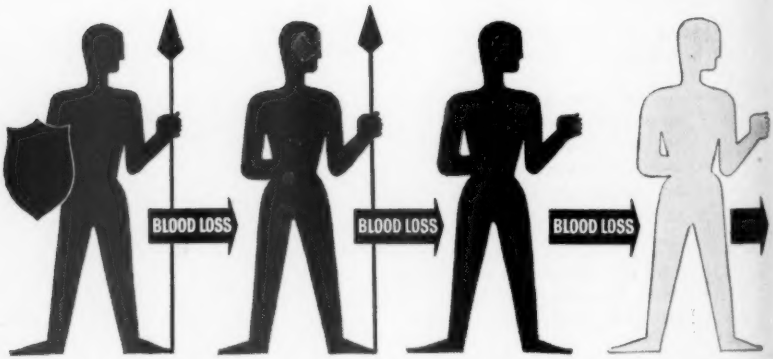

Haemoglobin normal	*Haemoglobin normal*	*Haemoglobin normal*	*Haemoglobin down*
Body iron stores normal	*Body iron stores falling*	*Body iron stores exhausted*	*Body iron stores still exhausted*

Suggested further reading:

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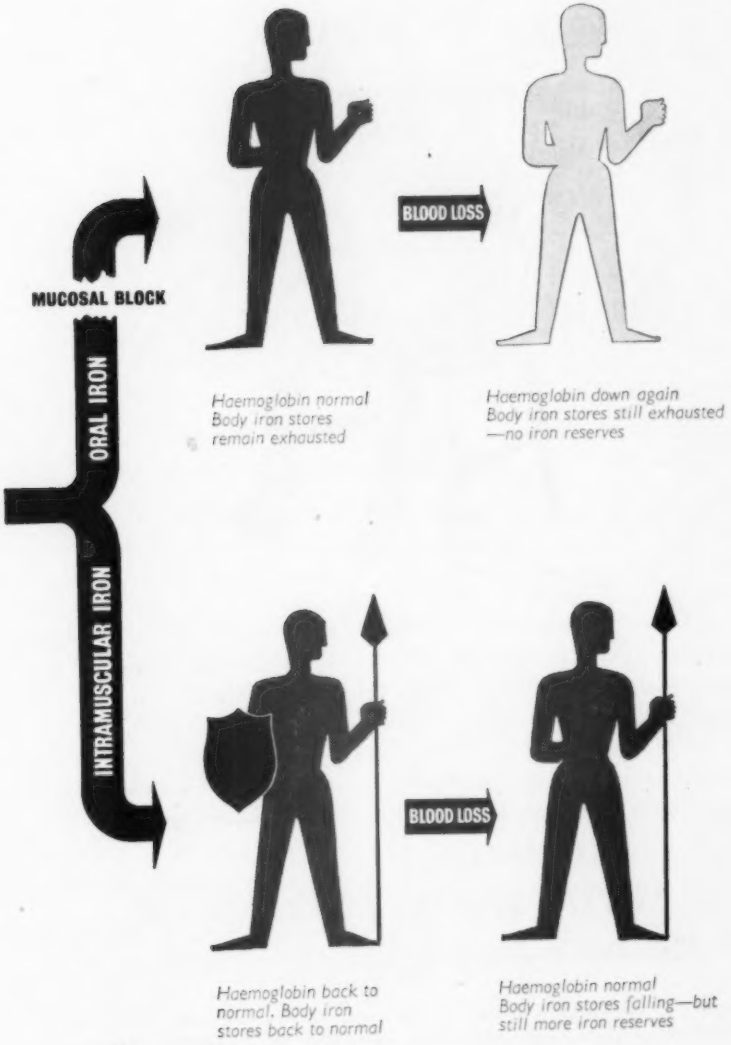

Haemoglobin normal
Body iron stores remain exhausted

Haemoglobin down again
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Haemoglobin back to normal. Body iron stores back to normal

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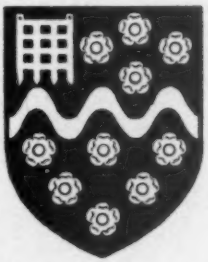

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* "*Treatment of Haemorrhoids*"—*Practitioner, Vol. 178, Feb. 1957*

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FOR THE ORAL TREATMENT OF PILES AND ALLIED CONDITIONS

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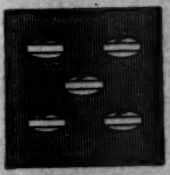

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